

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number  
**WO 02/066459 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 401/12**,  
A61K 31/404, A61P 5/02, C07D 409/12, 209/16, 417/12,  
403/12, 401/14

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(21) International Application Number: PCT/GB02/00679

(22) International Filing Date: 15 February 2002 (15.02.2002)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0100566-9 20 February 2001 (20.02.2001) SE

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VN, YU, ZA, ZM, ZW.

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BF, BG, BJ, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ,  
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GM, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP,  
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK,  
MN, MW, MX, MZ, NL, NO, NZ, OM, PH, PL, PT, RO, RU,  
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(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

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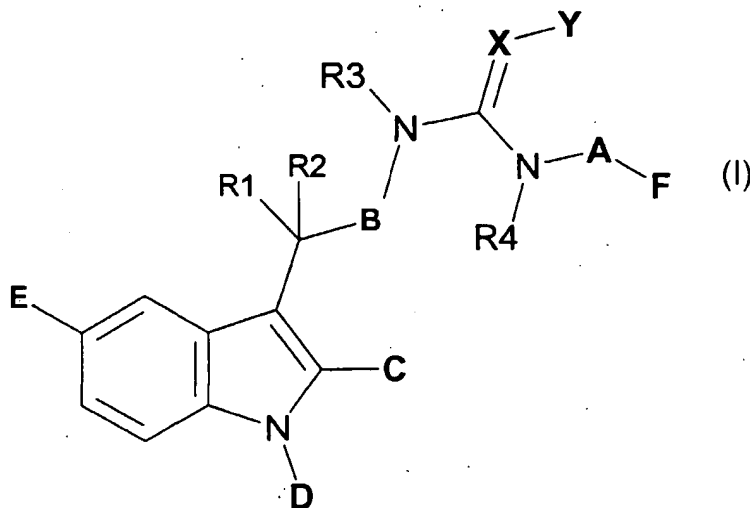
Published:  
— with international search report

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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: INDOLE DERIVATIVES AND THEIR USE AS GNRH ANTAGONISTS



(57) Abstract: The present invention relates to compounds of formula (I) which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

WO 02/066459 A1

## INDOLE DERIVATIVES AND THEIR USE AS GNRH ANTAGONISTS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical  
5 formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

10 BACKGROUND TO THE INVENTION

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-  
15 stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberein, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of  
20 their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

25 It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

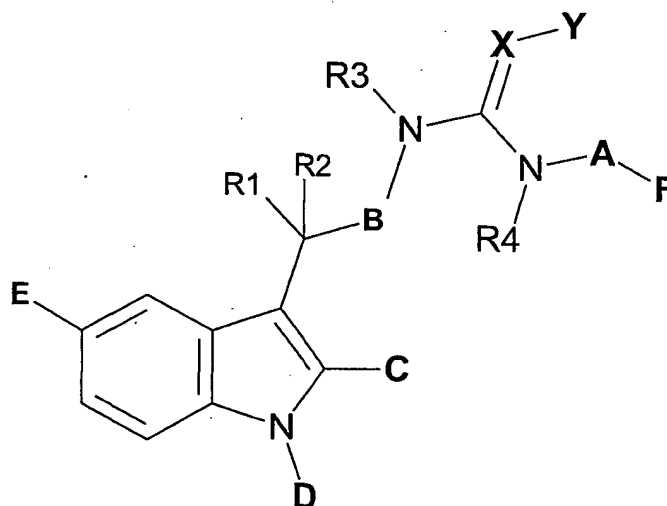
The following disclose compounds purported to act as GnRH antagonists: WO 00/04013, WO 99/41252, WO 99/41251, WO 98/55123, WO 97/21704, WO 97/21703, WO 97/21707, WO 97/21435, WO 97/44041, WO 98/55119, WO 99/51596 and WO 97/14697.

- 5 It would be desirable to provide further compounds, such compounds being GnRH antagonists.

### SUMMARY OF THE INVENTION

10

The present invention accordingly provides a compound of formula I or a pharmaceutically acceptable salt or solvate thereof



15

For A, either:-

- (i) A represents a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or  $-R-Ar-R'$ -, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl; or
- 20

(ii) the structure N-A(-R4) represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S, N-A(-R4) being optionally substituted;

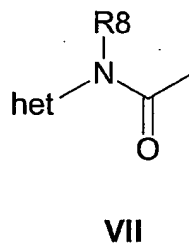
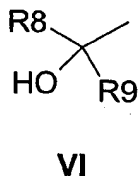
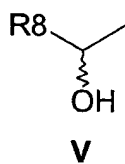
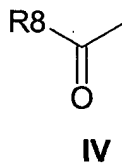
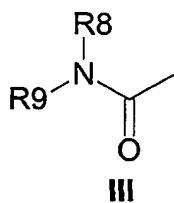
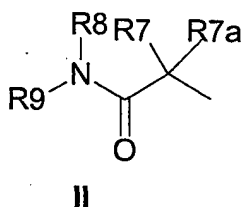
5 **B** represents a bond or optionally substituted C1 to C5 alkylene;

**C** represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR<sub>5</sub>R<sub>6</sub>; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen;

10

**D** represents hydrogen; optionally substituted C1 to C8 alkyl; or (CH<sub>2</sub>)<sub>b</sub>-R, wherein R represents C3 to C8 cycloalkyl;

**E** is selected from an optionally substituted 3- to 8- membered heterocyclic ring containing  
15 from 1 to 4 heteroatoms independently selected from O, N and S; **II**; **III**; **IV**; **V**; **VI** and **VII**



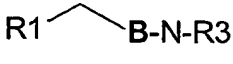
20 wherein het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

F is optionally substituted and represents phenyl or a 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

For X and Y, either:-

- 5 (iii) X represents N and Y represents CN or H; or X represents CH and Y represents NO<sub>2</sub>; or  
(iv) X-Y represents O;

For R1 and R2, either:-

- 10 (v) R1 and R2 are independently selected from hydrogen and optionally substituted C1 to C8 alkyl; or  
(vi) R1 and R2 together represent carbonyl; or  
(vii)  represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected  
15 from O, N and S, and R2 meets the definition in option (v);

R3 meets the definition in option (vii) or represents hydrogen or optionally substituted C1 to C8 alkyl;


- 20 R4 meets the definition in option (ii) or represents hydrogen or optionally substituted C1 to C8 alkyl;

R5 and R6 are independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

25

For R7 and R7a, either:-

- (viii) R7 and R7a are independently selected from H or optionally substituted C1 to C8 alkyl; or

(ix)  represents an optionally substituted 3 to 7-membered cycloalkyl ring;


For R8 and R9, either:-

5 (x) R8 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; -R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and

10 R9 is selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl; or

(xi) wherein E represents structure **II** or **III**, NR8(-R9) represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

15 (xii) wherein E represents structure **VI**,

 represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

20 b represents zero or an integer from 1 to 6.

In one embodiment, a compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof is provided, with the proviso that a compound wherein X represents CH, Y represents NO<sub>2</sub>, N-A(-R4) meets the definition in option (ii) and F represents optionally substituted phenyl is excluded.

25

The present invention also provides a pharmaceutical formulation comprising such a compound and a pharmaceutically acceptable diluent or carrier.

30 Furthermore, the present invention provides the following uses of the compound:-

- (a) Use in the manufacture of a medicament, for antagonising gonadotropin releasing hormone activity.
- 5 (b) Use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.
- (c) Use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

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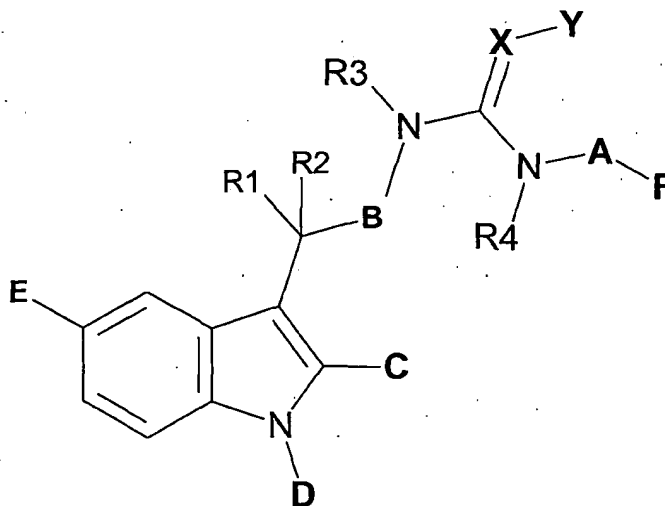
The present invention also relates to a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering the compound to the patient.

In addition, the invention provides a process of producing the compound.

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### DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the present invention provides a compound of formula I or a  
20 pharmaceutically acceptable salt or solvate thereof

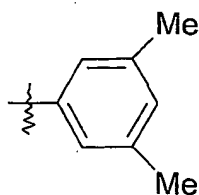


For A, either:-

- (i) A represents a single bond; optionally substituted C1 to C8 alkylene (preferably, C1 to C4 alkylene, for example methylene or ethylene); a C2 to C12 (preferably, C2 to C8) group having at least one (eg, 1, 2 or 3) alkene double bond; or  $-R-Ar-R'$ , where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene (preferably, C1 to C4 alkylene, for example methylene or ethylene) and a C2 to C12 (preferably, C2 to C8) group having at least one (eg, 1, 2 or 3) alkene double bond; and Ar represents optionally substituted aryl (eg, optionally substituted phenyl); or
- (ii) the structure N-A(-R4) represents a 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) optionally containing from 1 to 3 (eg, 1) further heteroatoms independently selected from O, N and S, N-A(-R4) being optionally substituted.
- B represents a bond or optionally substituted C1 to C5 alkylene (preferably, C1 to C4 alkylene, for example methylene or ethylene).

C represents a mono- or bi-cyclic aromatic ring structure (preferably, phenyl) optionally having at least one substituent (eg, 1, 2 or 3 substituents) selected from CN; NR<sub>5</sub>R<sub>6</sub>; an optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, eg, methyl); optionally substituted C1 to C8 alkoxy (preferably, C1 to C6 alkoxy, eg, methoxy); halogen (eg, F, Br or Cl).

Preferably, C represents

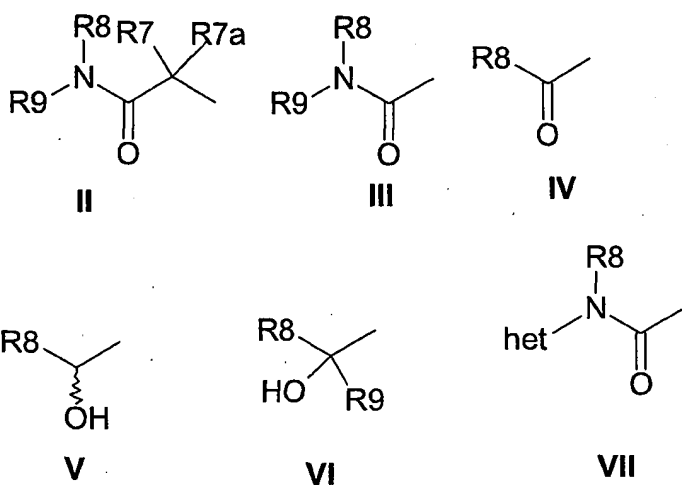


wherein Me represents methyl.



**D** represents hydrogen; optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl); or  $(CH_2)_b-R$ , wherein R represents C3 to C8 cycloalkyl (eg, C3, C4, C5 or C6 cycloalkyl).

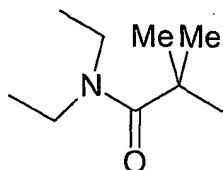
- 5 **E** is selected from an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 4 (eg, 1 or 2) heteroatoms independently selected from O, N and S; **II**; **III**; **IV**; **V**; **VI** and **VII**



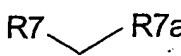
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wherein het represents an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 4 (eg, 1 or 2) heteroatoms independently selected from O, N and S.

- 15 Preferably, **E** represents  
(a)



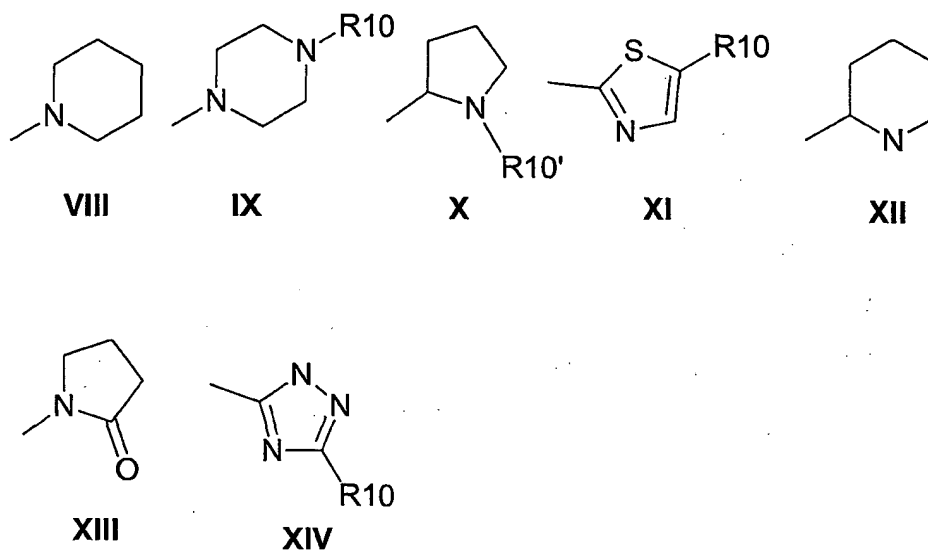
wherein Me represents methyl; or

(b) structure II, wherein  represents cyclopropyl or cyclobutyl.

F is optionally substituted and represents phenyl or a 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 4 (eg, 1 or 2)

5 heteroatoms independently selected from O, N and S.

Preferably, F is optionally substituted and represents pyridyl, VIII, IX, X, XI, XII, XIII or XIV



10

wherein

R10 represents hydrogen; optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl); OH; halogen (eg, F, Cl or Br); CN; C1 to C8 alkoxy (preferably, C1 to C6

15 alkoxy, eg, methoxy); or CF<sub>3</sub>; and

R10' represents hydrogen or optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl).

For X and Y, either:-

20 (iii) X represents N and Y represents CN or H; or X represents CH and Y represents

NO<sub>2</sub>; or

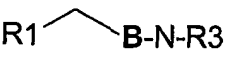
(iv) X-Y represents O.

For R1 and R2, either:-

(v) R1 and R2 are independently selected from hydrogen and optionally substituted C1 to

5 C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl); or

(vi) R1 and R2 together represent carbonyl; or

(vii)  represents an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 3 (eg, 1 or 2) further heteroatoms independently selected from O, N and S, and R2 meets the definition in option (v).

10

In one embodiment, R1 and R2 each represent H and B represents C1 alkylene.

R3 meets the definition in option (vii) or represents hydrogen or optionally substituted C1

15 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl).

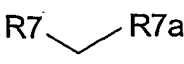
R4 meets the definition in option (ii) or represents hydrogen or optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl).

20 R5 and R6 are independently selected from H; optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl); and optionally substituted aryl (eg, phenyl).

For R7 and R7a, either:-

(viii) R7 and R7a are independently selected from H or optionally substituted C1 to C8 alkyl (preferably, C1 to C6 alkyl, eg, methyl; in one embodiment R7 and R7a are both methyl); or

25

(ix)  represents an optionally substituted 3 to 7-membered (eg, 3-, 4-, 5- or 6-membered) cycloalkyl ring;

30



- O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C1 to C6 alkyl), preferably Omethyl or O(C2 to C4 alkyl); halo, preferably Cl or F; CHal<sub>3</sub>, CHHal<sub>2</sub>, CH<sub>2</sub>Hal, OCHal<sub>3</sub>, OCHHal<sub>2</sub> or OCH<sub>2</sub>Hal, wherein Hal represents halogen (preferably F); CH<sub>2</sub>OR, NRCOR', NRSO<sub>2</sub>R' or N-R-R', wherein R and R' independently represent H or C1 to C8 alkyl
- 5 (preferably methyl or C2 to C6 alkyl or C2 to C4 alkyl), or N-R-R' represents an optionally substituted C3 to C8, preferably C3 to C6, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; H; or COOR'' or COR'', R'' representing H, optionally substituted phenyl or C1 to C6 alkyl (preferably methyl, ethyl, *i*-propyl or *t*-butyl). For optional substitution of the heterocyclic
- 10 ring represented by N-R-R', at least one (eg, one, two or three) substituents may be provided independently selected from C1 to C6 alkyl (eg, C2 to C4 alkyl, more preferably methyl); phenyl; OCF<sub>3</sub>; OCHF<sub>2</sub>; -O(C1-C8 alkyl), preferably -O-methyl, -O-ethyl or -O(C3 to C6 alkyl); -C(O)O(C1-C8 alkyl), preferably -C(O)O-methyl, -C(O)O-ethyl, -C(O)O-*tert*-butyl or -C(O)O(C3 to C6 alkyl); -C(O)O-phenyl; -O-phenyl; -C(O) (C1-C8
- 15 alkyl), preferably -C(O)-methyl, -C(O)-ethyl or -C(O)(C3 to C6 alkyl); -C(O)OH; -S(C1-C8 alkyl), preferably -S-methyl, -S-ethyl or -S(C3 to C6 alkyl); OH; halogen (eg, F, Cl or Br); NR\*R\*\* where R\* and R\*\* are independently H or C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.
- 20 Where optional substitution of a ring is mentioned at various places, this most preferably refers to one, two, three or more substituents selected from C1 to C8 alkyl (eg, C2 to C6 alkyl, and most preferably methyl); -O(C1 to C8 alkyl), preferably -O-methyl, -O-ethyl or -O(C3 to C6 alkyl); halogen (eg, F, Cl or Br); CN; and NO<sub>2</sub>.
- 25 Particularly preferred compounds according to the present invention are:-
- 2-(2-(3,5-dimethylphenyl)-3-{2-[(2-nitro-1-{[2-(4-pyridinyl)ethyl]amino}ethenyl)amino]ethyl}-1H-indol-5-yl)-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[2-(4-pyridinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[2-(2-pyridinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[2-(1-imidazolyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[2-(3,5-dimethylphenyl)-3-(2-{[(phenethylamino)carbonyl]amino}ethyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[2-(3,5-dimethylphenyl)-3-(2-{[(4-pyridinyl)ethyl]amino}carbonyl]amino}ethyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[3-(4-methylpiperazino)propyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[2-(2-piperidinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[(cyanoimino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl]amino}ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[[(cyanoimino){[2-(4-pyridinyl)ethyl]aminomethyl}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2-{[2-nitro-1-([3-(4-pyridinyl)-pyrrolidin-1-yl]ethenyl]amino}ethyl)-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-[2-((carbonyl)[3-(4-pyridinyl)-pyrrolidin-1-yl]amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

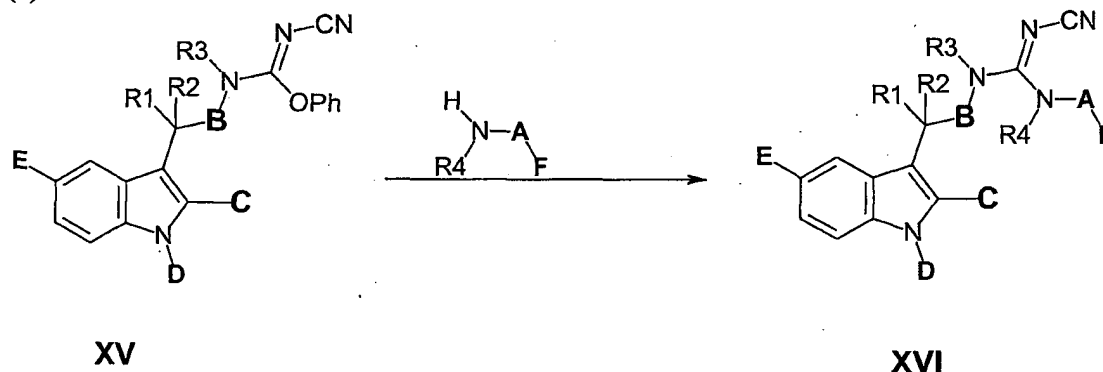
2-[3-[2-((imino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl} amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide; and

2-[3-[2-((cyanoimino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl} amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-1-cyclopropylcarboxylic acid-diethylamide.

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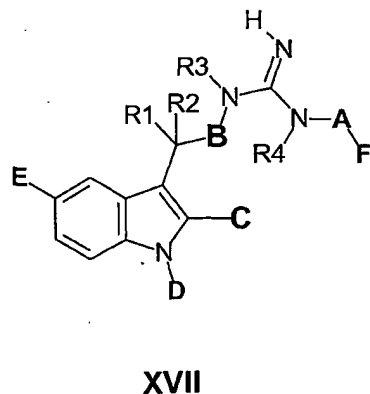
The compounds of formula I can be prepared by a process comprising a step selected from (a) to (e) as follows:-

(a) Reaction of XV as follows

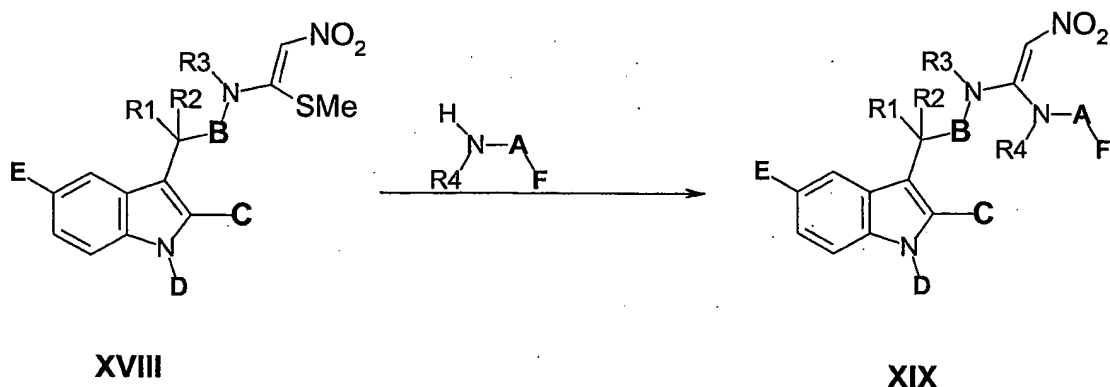


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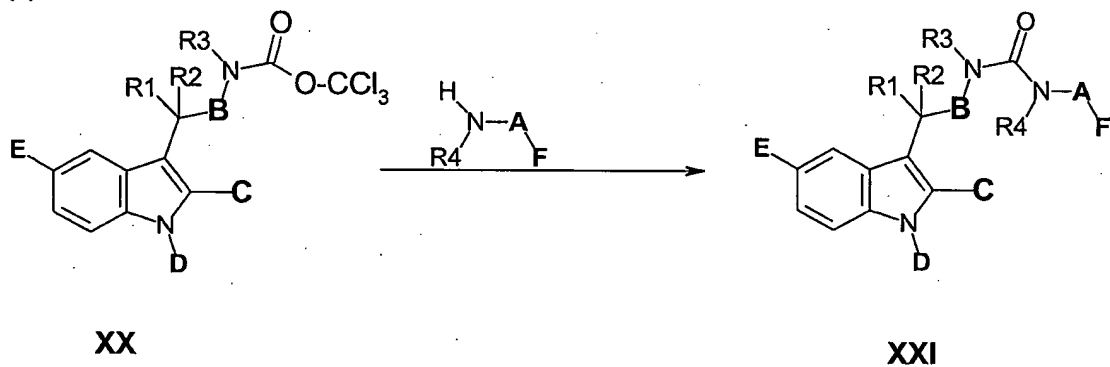
(b) Cleavage of the CN group of XVI in the presence of acid to produce XVII



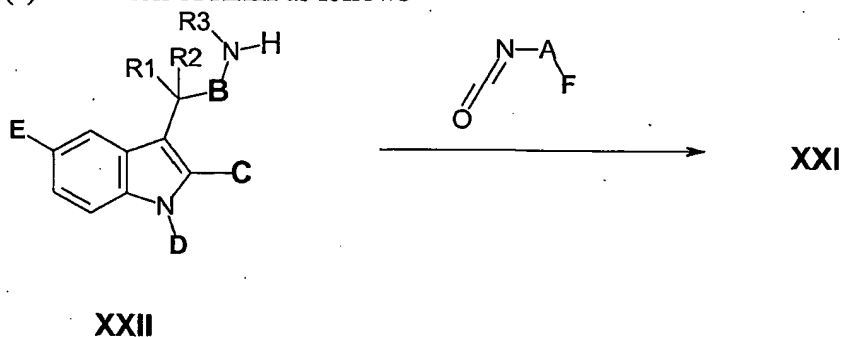
(c) Reaction of XVIII as follows



(d) Reaction of XX as follows



(e) Reaction of XXII as follows



It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus,



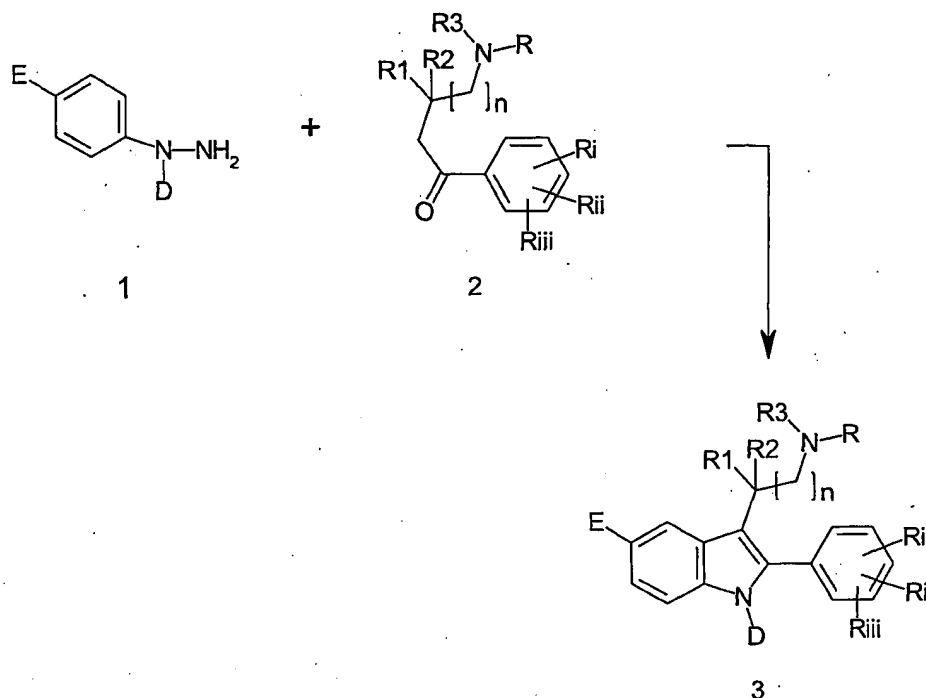
the preparation of the compounds of formula I may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The invention also contemplates pharmaceutically acceptable salts and solvates of compounds of formula I.

**EXPERIMENTAL****GENERAL REACTION SCHEMES**

- 5 In the following schemes, group C has been depicted as substituted phenyl for illustration purposes only. Other definitions of C are also appropriate.

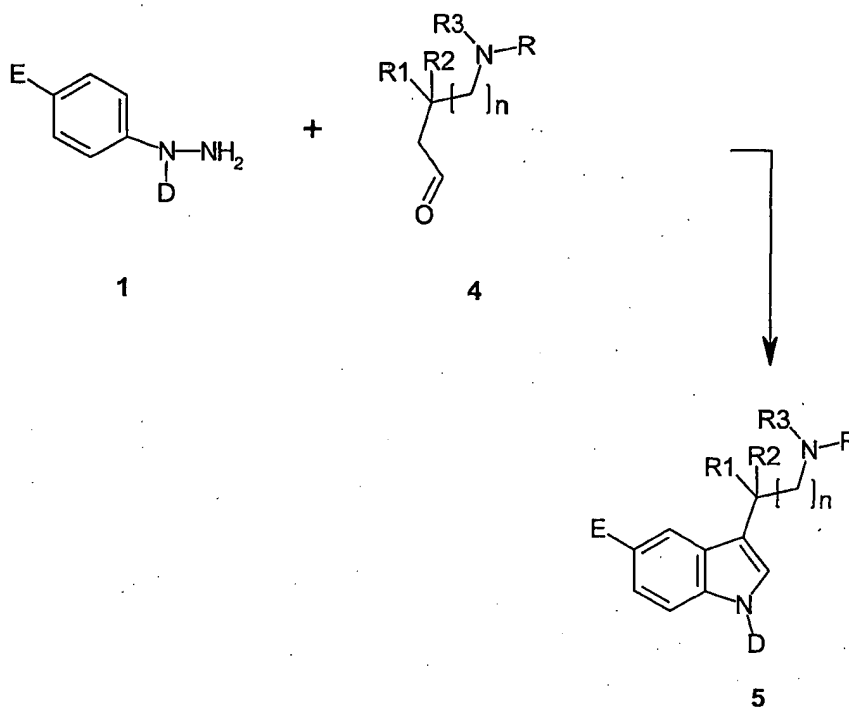


Scheme a. Fischer indole synthesis.

10

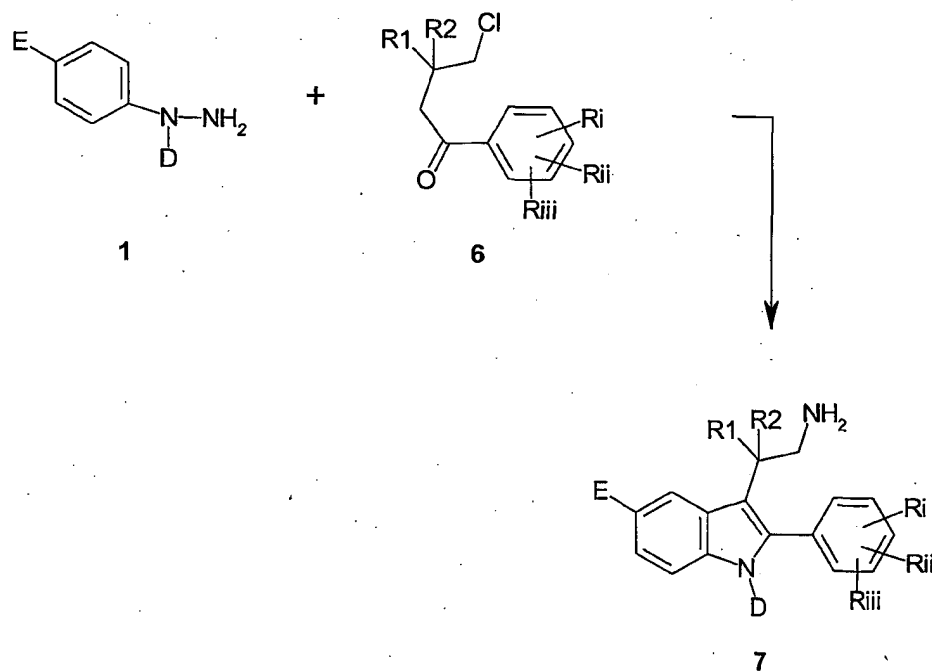
- Tryptamines, such as 3 can be synthesised by the classic Fisher indole synthesis reaction by the condensation of a hydrazine 1 and a ketone 2, bearing hydrogen atoms  $\alpha$  to the carbonyl (Scheme a). Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *tert*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. R represents a protecting group, eg *tert*-butylcarbamate or phthalimide.
- 15

18



Scheme b

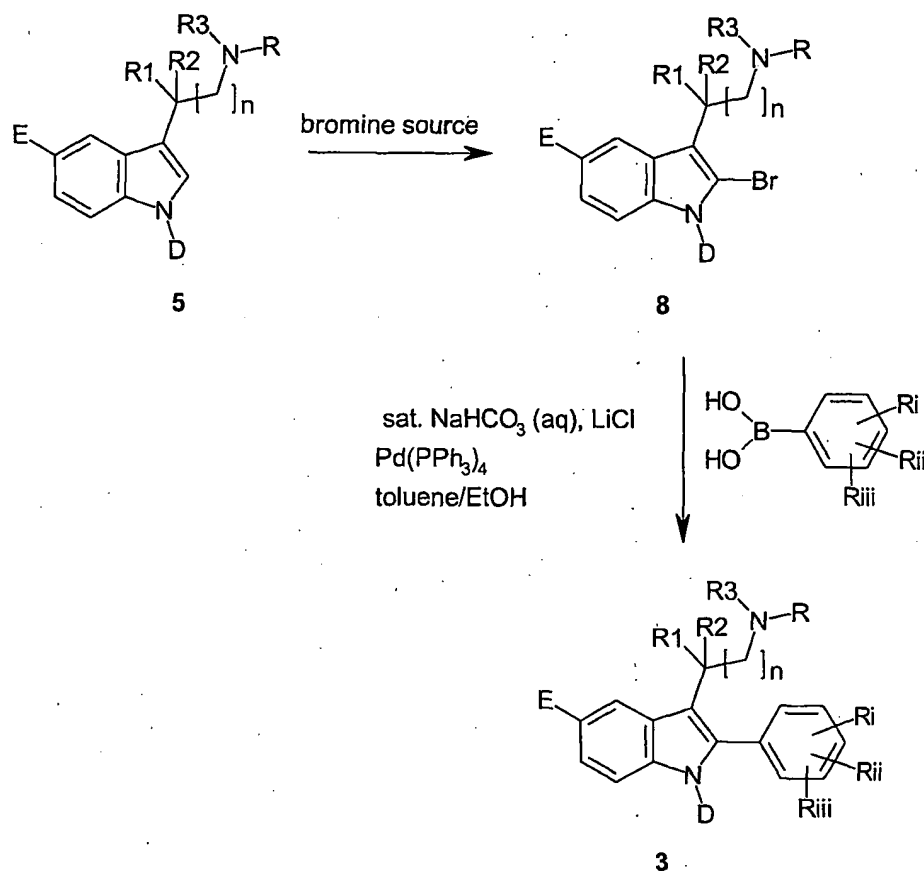
Tryptamines, such as represented in structure 5, can also be made using aldehydes 4, bearing hydrogen atoms  $\alpha$  to the carbonyl, by cyclisation using the conditions above. In this case the substituent at the 2-position must be added later (see scheme d).



Scheme c

Tryptamine may also be synthesised utilising the Granburg reaction, wherein a hydrazine **1** is mixed with ketone **6**, bearing a chlorine atom  $\gamma$  to the carbonyl, and heated in a suitable solvent such as ethanol, tert-butanol, toluene at a temperature between 50 °C and 120 °C (Scheme c).

5

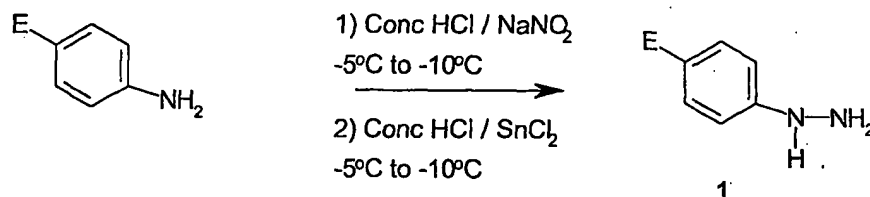


Scheme d

The tryptamine **5** can be treated with a 'bromine source', such as molecular bromide, pyridinium tribromide, pyrrolidone hydrobromide or polymer supported reagent equivalents, in an inert solvent such as chloroform, methylene chloride at -10 °C to 25 °C to yield the 2-bromo compound **8** (Scheme d). Reaction under Suzuki conditions with a palladium(0) catalyst, a weak base such aqueous sodium carbonate or saturated sodium hydrogen carbonate and the like, and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF

15

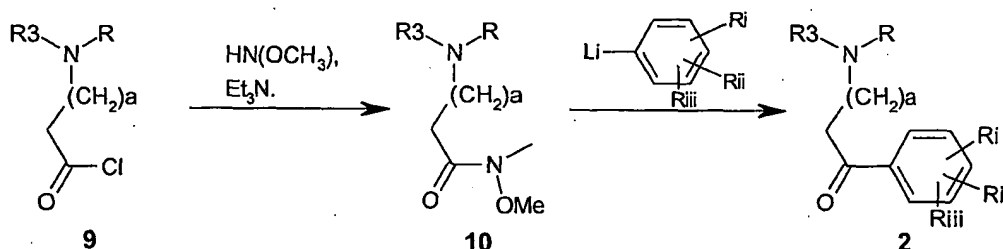
and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the desired compound 3.



5

The hydrazines 1 can be purchased from commercial sources either as a free base or suitable salt (e.g. hydrochloride), which are both acceptable under the reaction conditions. Hydrazines may be synthesised by the two-step process of diazotisation of an aniline, under the preferred conditions of concentrated hydrochloric acid sodium nitrite at a temperature between -10 °C and -5 °C, then reduction under the preferred conditions of tin(II) chloride in concentrated hydrochloric acid at a temperature between -10°C and -5°C.

10



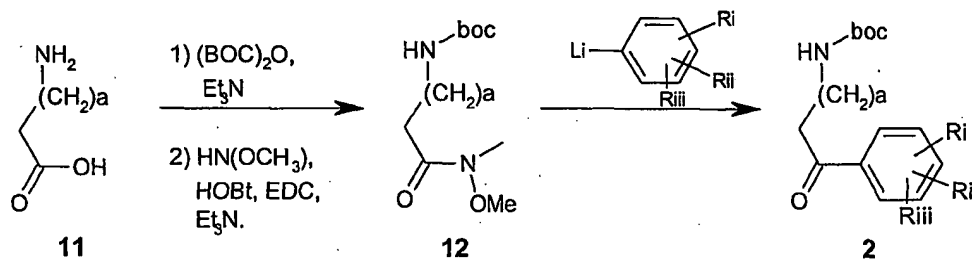
Scheme e.

15

Substituted ketones 2 can be prepared, as outlined in Scheme e starting from appropriate acid chlorides such as 9. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine hydrochloride in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide 10. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, 1988, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then

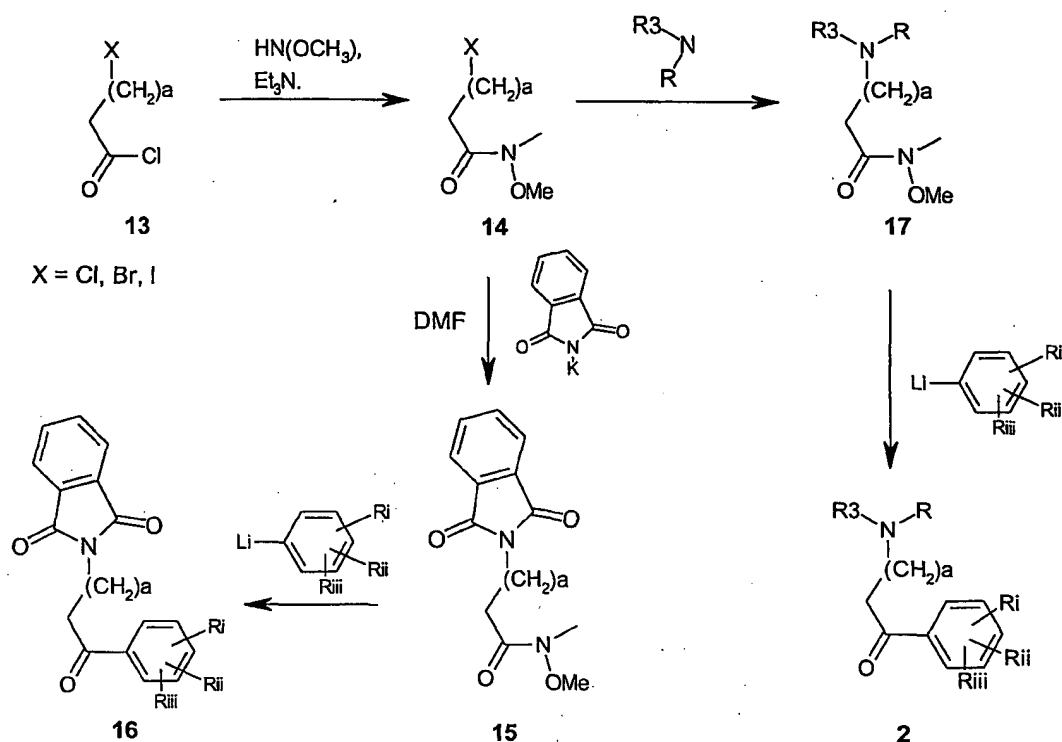
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quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **2**.



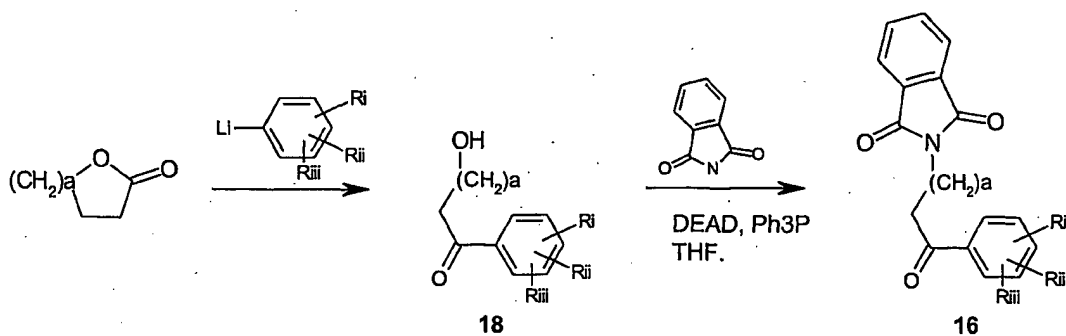
Scheme f.

Commencing with a readily available amino acid with a suitable chain length [a] **11**, the nitrogen atom can be brought in at the beginning of the synthesis by the route shown in Scheme f. Protection of the amine group of **11** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl dicarbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C. Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBT), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 h provided the corresponding coupled product **12**. Following the same route described above for scheme d, the aryl group can then be installed.



Scheme g.

Scheme g illustrates another method for the synthesis of ketone such as **2** and **16**, where the nitrogen group is introduced at a latter stage. As above a Weinreb amide **14** can be synthesised from an acid chloride. Treatment with the required amine, in an inert solvent such as THF, toluene, water and the such like can displace the group X to give **17**. As above the aryl group can be introduced by displacement of the Weinreb amide with a suitable aryl lithium nucleophile. Alternatively the nitrogen atom can be introduced already protected as a phthalimide by displacement of the group x by potassium phthalimide, or similar salt thereof, by heating in an inert polar solvent such as DMF, DMSO, THF, toluene with or without the presence of a catalyst such as tetrabutylammonium iodide and the such like, to yield the compound **15**. Again displacement of the Weinreb amide with an organolithium species completes the synthesis of a ketone suitable for cyclisation under the Fischer condition described above for indole synthesis.



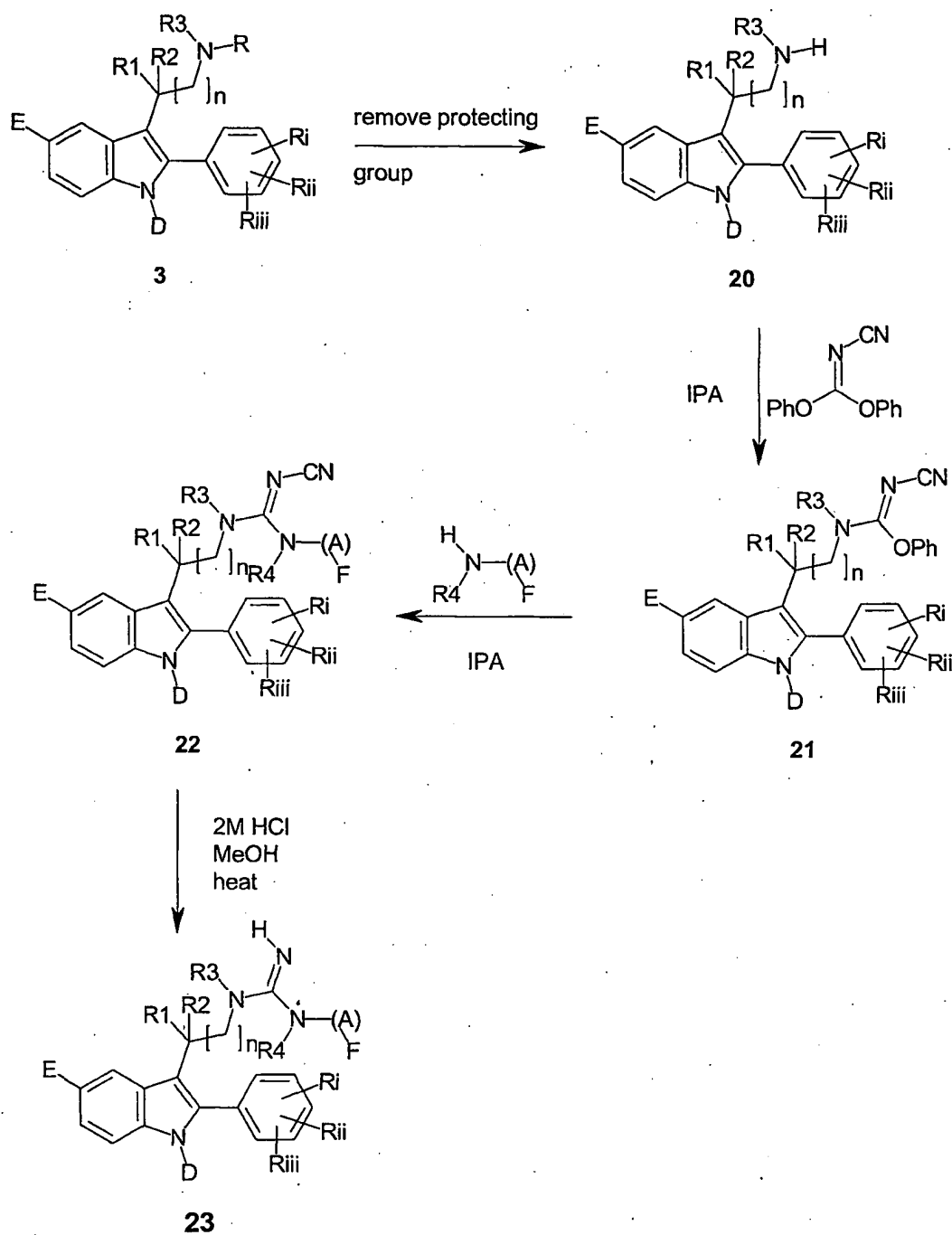
Scheme h.

An alternative approach to a phthalimide protected nitrogen ketone, such as 16, can be taken by firstly treating a lactone, with an organolithium species as in the above schemes in a suitable solvent such as THF or ether at a low temperature of between  $-100^\circ\text{C}$  and  $-50^\circ\text{C}$  to yield a primary alcohol 18 (Scheme h). The hydroxyl function of 18 is replaced with a phthalimide group by a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the desired ketone 16.



If the group D was not present on the starting hydrazine before cyclisation to form an indole it may be added post cyclisation by an alkylation reaction (19 $\rightarrow$ 3). The indole is deprotonated by a strong base, such as sodium hydride, *n*-butyl lithium, lithium diisopropylamine, sodium hydroxide, potassium *tert*-butoxide in a suitable inert solvent such as THF, DMF, DMSO and the such like, and an alkyl halide added and the mixture stirred at room temperature.

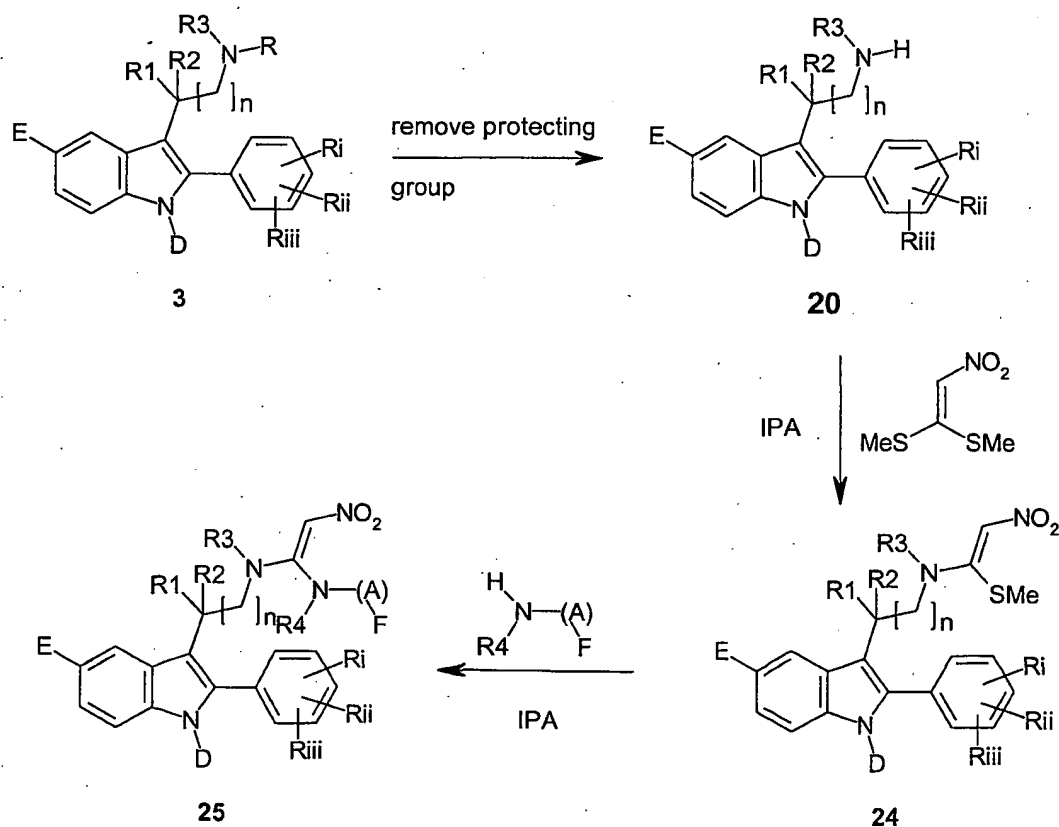




Scheme i

Depending on the route used above a tryptamine 20 suitable for conversion to a cyano-guandine can be formed by removal of the protecting group, for example if a *tert*-butylcarbamate group was used then removal is accomplished using a strong acid, for example trifluoroacetic acid or hydrochloric acid in an inert solvent such as methylene chloride, chloroform, THF or dioxane at a temperature between -20°C and 25°C. A

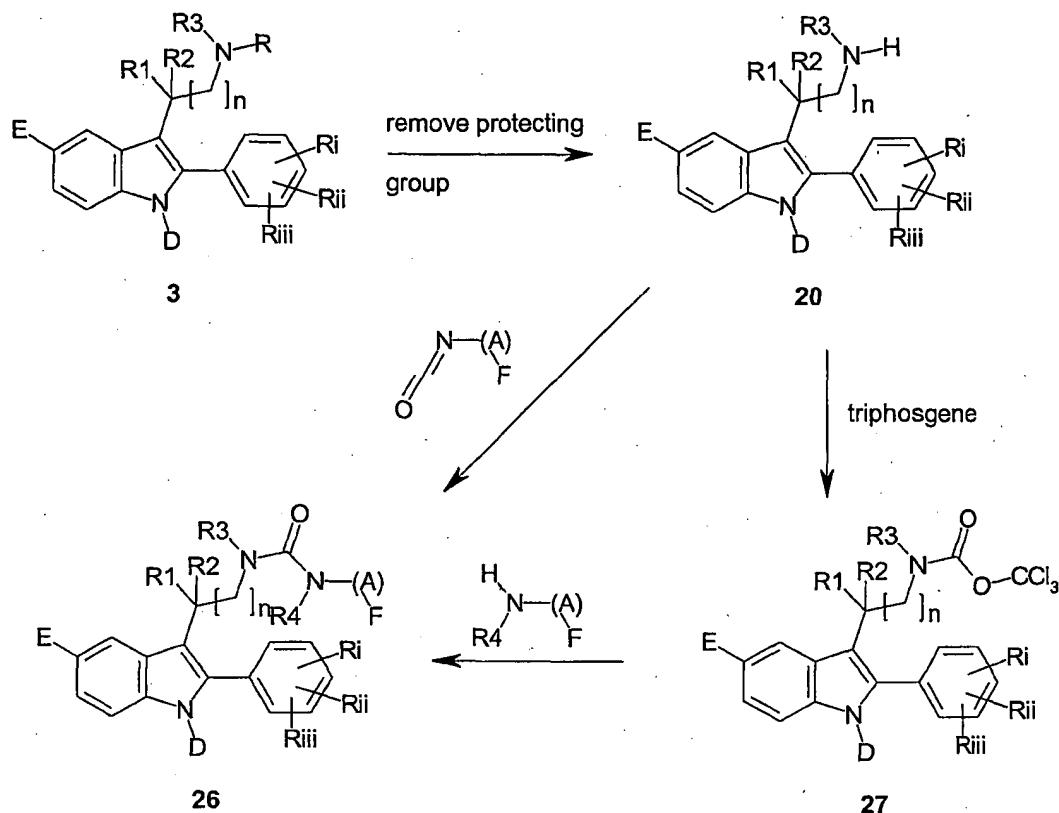
phthalimide group, for example, can be removed by hydrazine in a suitable solvent for example methanol, ethanol, methylene chloride, chloroform, THF dioxane at a temperature between -20°C and 25°C. The primary amine **20** can be converted to a cyano-guanidine **22** by the two step process of reaction with diphenyl cyanocarbonimide in an inert organic solvent such as isopropyl alcohol, methylene chloride, chloroform, benzene, tetrahydrofuran and the like, at a temperature between -20°C and 50°C, followed by condensation with an appropriately substituted amine in an inert organic from the list above, with heating at a temperature between -20°C and 100°C (Scheme I **20**→**21**→**22**). Further treatment of **22** with 2 molar Hydrochloric acid in methanol at elevated temperature yields guanidine compounds **23**.



Scheme j.

Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by

condensation with an appropriately substituted amine in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25** (Scheme j, **20**→**24**→**25**).



Scheme k.

Again in a similar fashion the suitable tryptamine **20**, derived from deprotection, can be converted to a urea by either direct treatment with an iso-cyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**20**→**27**) followed by addition of an amine (**27**→**26**), bearing the required substitution to yield **26**.

**EXAMPLES****Example 1**

See Scheme 1 below for more details.

- 5 4 - Pyrrolidin -3 - yl pyridine (1.00g, 6.76 mmol) was added to a stirred suspension of L (1.00g, 1.80mmol) in IPA (5ml) and the mixture heated at reflux for 36 hours. The RM was concentrated in vacuo and the residues purified by chromatography on SiO<sub>2</sub> (Isolute, 50g), eluting with a gradient 0-10% MeOH /CH<sub>2</sub>Cl<sub>2</sub> to give **1** as a white foam 672mg(61%).

10

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.80 (m,3H) ; 1.00-1.20 (m,3H) ; 1.60 (s,6H) ; 1.80-2.00(m,1H) ; 2.10-2.30 (m,1H) ; 2.35 (s,6H) ; 2.80-3.00 (m,2H) ; 3.10 -3.50 (m, 8H) ; 3.60-3.80 (m,3H) ; 4.40 (m,1H) ; 6.97 (s,1H) ; 7.00-7.15 (m,3H) ; 7.20 (s,2H) ; 7.28-7.36 (m,1H) ; 7.41 (s,1H) ; 8.22 (s,1H) ; 8.48-8.60 (m,2H).

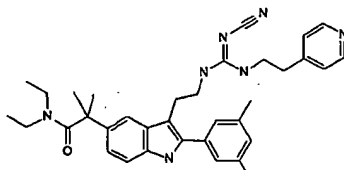
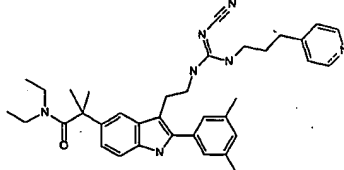
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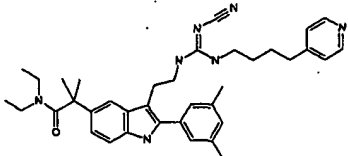
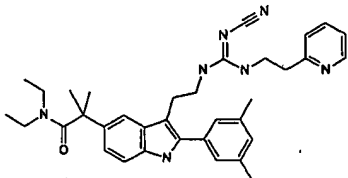
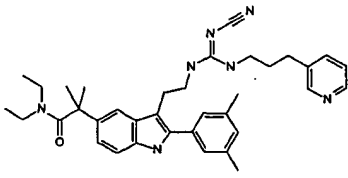
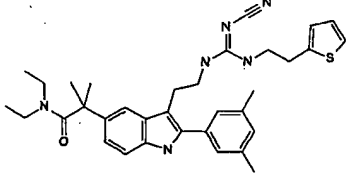
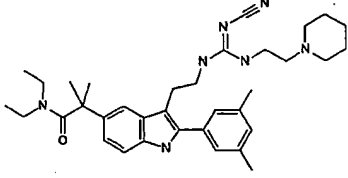
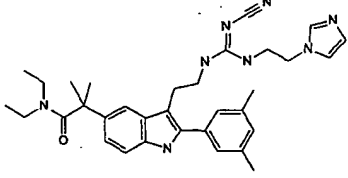
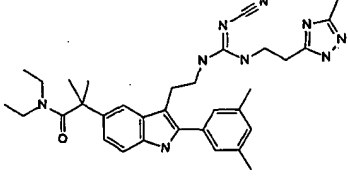
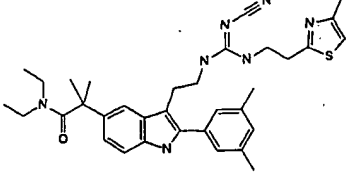
MS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 604.56

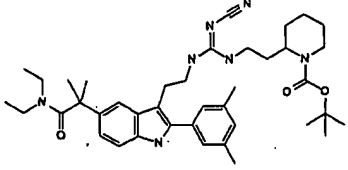
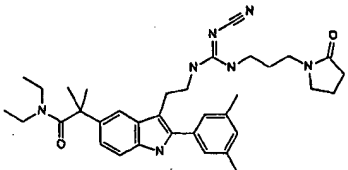
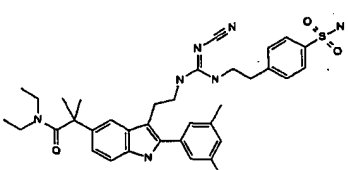
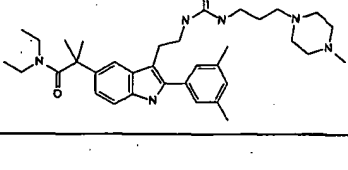
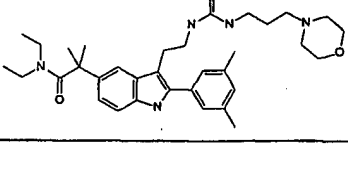
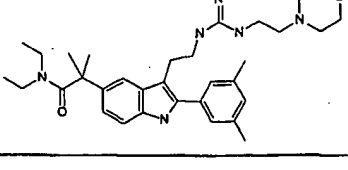
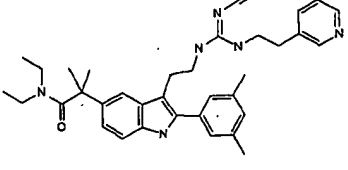
MS (ES<sup>-</sup>) m/z (M-H)<sup>-</sup> 602.54

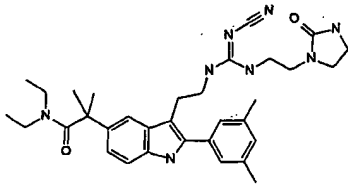
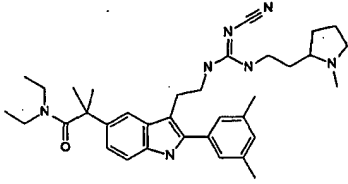
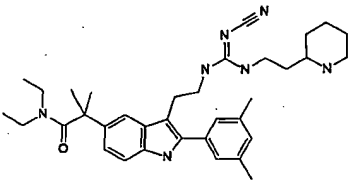
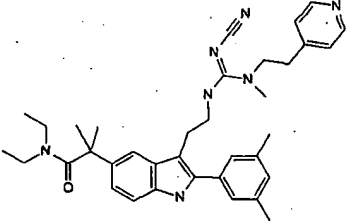
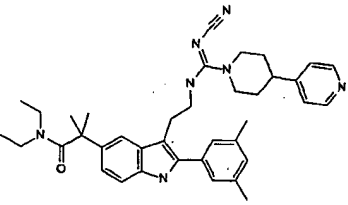
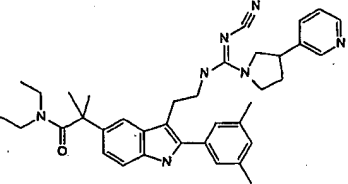
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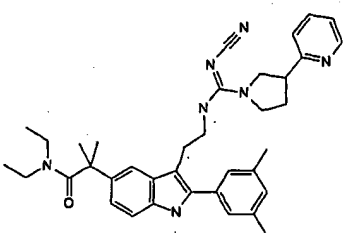
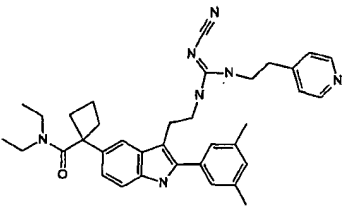
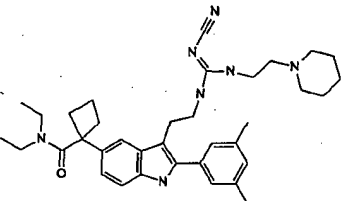
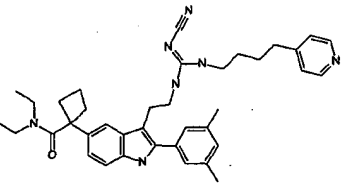
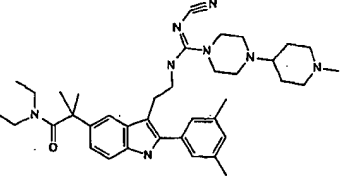
Following a procedure similar to that described in Example 1, the following compounds were prepared.

STRUCTURE	EXAMPLE	MS (ES) <sup>+</sup>
	1.01	578.74(M+H) <sup>+</sup>
	1.02	592.44(M+H) <sup>+</sup>

	1.03	606.76(M+H)+
	1.04	578.72(M+H)+
	1.05	592.74(M+H)+
	1.06	583.70(M+H)+
	1.07	584.79(M+H)+
	1.08	567.74(M+H)+
	1.09	582.74(M+H)+
	1.10	598.71(M+H)+

	1.11	648.99(M+H)+
	1.12	598.86(M+H)+
	1.13	656.84(M+H)+
	1.14	613.93(M+H)+
	1.15	600.89(M+H)+
	1.16	586.85(M+H)+
	1.17	578.7(M+H)+

	1.18	585.83(M+H)+
	1.19	584.87(M+H)+
	1.20	584.54(M+H)+
	1.21	592.53(M+H)+
	1.22	618.55(M+H)+
	1.23	604.6(M+H)+

	1.24	604.54(M+H)+
	1.25	590.76(M+H)+
	1.26	596.78(M+H)+
	1.27	618.58 (M+H)+
	1.28	639.73(M+H)+



**EXAMPLE 2**

See Scheme 2 below for more details.

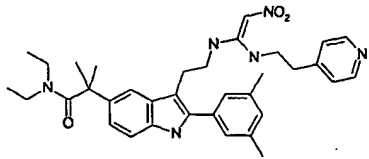
4 - Pyrrolidin -3 - yl pyridine (148mg, 1.00 mmol) was added to a stirred suspension of M  
 5 (105mg, 0.20mmol) in IPA (5ml) and the mixture heated at reflux for 48 hours. The RM  
 was concentrated in vacuo and the residues purified by chromatography on SiO<sub>2</sub> (Isolute,  
 50g), eluting with a gradient 0-20% MeOH /EtOAc to give **2** as a tan foam 71.0mg(57%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.45-0.65 ( m,3H) ; 0.85-1.05 (m,3H) ; 1.45 (d,6H) ; 1.70-  
 10 1.90 (m,1H) ; 2.00-2.20 (m,1H) ; 2.20 (s,6H) ; 2.60-2.90 (m,2H) ; 3.00 -3.30 (m, 8H) ;  
 3.30-3.50 (m,3H) ; 6.28 (s,1H) ; 6.80-7.00 (m,6H) ; 7.10-7.25 (m,2H) ; 8.05 (s,1H) ; 8.37  
 (d,2H) ; 9.90 (t,1H).

MS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 623.28

15 MS (ES<sup>-</sup>) m/z (M-H)<sup>-</sup> 621.23

Following a procedure similar to that described in Example 2, the following compound  
 was prepared.

STRUCTURE	EXAMPLE	MS (ES)+
	2.01	597.57(M+H)+

**Example 3**

See Scheme 3 below for more details.

- 5 A solution of K (100mg, 0.25mmol) and Diisopropyl ethylamine (36.0mg, 0.25mmol) in  $\text{CH}_2\text{Cl}_2$  (1ml) was added to a solution of Triphosgene (29.7mg, 0.10mmol) in  $\text{CH}_2\text{Cl}_2$  (1ml) and the mixture stirred for 15 minutes. A solution of Diisopropylethylamine (36.0mg, 0.25mmol) and 4 - Pyrrolidin -3 - yl pyridine (37.0mg, 0.25mmol) in  $\text{CH}_2\text{Cl}_2$  (1ml) was added and the mixture stirred for 60 hours. The RM was concentrated in-vacuo  
 10 and the residues purified by chromatography on  $\text{SiO}_2$  (Isolute, 50g), eluting with a gradient 0-10% MeOH /  $\text{CH}_2\text{Cl}_2$  to give 3 as a pale yellow foam 88.0mg(60%).

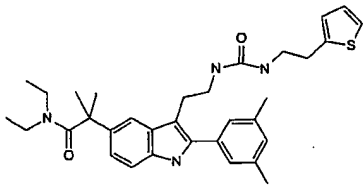
- $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 0.60-0.80 (m, 3H) ; 1.00-1.30 (m, 3H) ; 1.60 (s, 6H) ; 1.80-2.00 (m, 1H) ; 2.15-2.30 (m, 1H) ; 2.35 (s, 6H) ; 2.80-3.00 (m, 2H) ; 3.05 -3.45 (m, 8H) ;  
 15 3.50-3.70 (m, 3H) ; 4.20 (m, 1H) ; 6.85 (s, 1H) ; 7.00-7.10 (m, 3H) ; 7.22 (s, 2H) ; 7.30 (d, 1H) ; 7.45 (d, 1H) ; 8.12 (s, 1H) ; 8.50 (d, 2H).

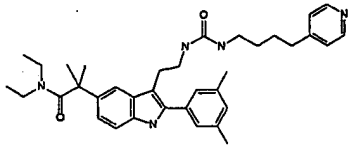
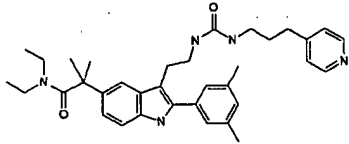
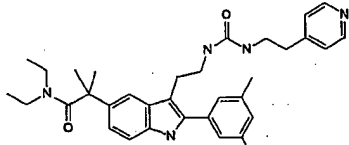
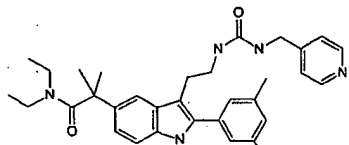
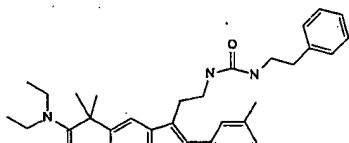
MS ( $\text{ES}^+$ ) m/z ( $\text{M}+\text{H}$ ) $^+$  580.72

MS ( $\text{ES}^-$ ) m/z ( $\text{M}-\text{H}$ ) $^-$  578.77

20

Following a procedure similar to that described in Example 3, the following compounds were prepared.

STRUCTURE	EXAMPLE	MS ( $\text{ES}$ ) $^+$
	3.01	559.56( $\text{M}+\text{H}$ ) $^+$

	3.02	582.3(M+H)+
	3.03	568.71(M+H)+
	3.04	554.68(M+H)+
	3.05	540.68(M+H)+
	3.06	553.38(M+H)+

**Example 4**

See Scheme 4 below for more details.

2N HCl (5ml) was added to a stirred solution of **1** (150mg, 0.22mmol) in MeOH (5ml) the  
5 resulting mixture was heated at 60°C for 18 hours. The RM was evaporated to dryness and  
the residues partitioned between saturated NaHCO<sub>3</sub> (100ml) and EtOAc (3 x 25ml).

Combined organics were concentrated in vacuo and the crudes purified by flash  
chromatography on SiO<sub>2</sub> (Isolute, 50g), eluting a gradient 0-25% MeOH /CH<sub>2</sub>Cl<sub>2</sub> to give **4**  
as a white solid 55.6mg (38.0%).

<sup>1</sup>H NMR (300MHz, DMSO-D<sub>6</sub>) 0.50-0.80 (m,3H) ; 0.90-1.10 (m,3H) ; 1.45 (s,6H) ;  
1.80-2.10 (m,1H) ; 2.20 -2.40 (m,1H); 2.30 (s,6H) ; 2.70-2.95 (m,2H) ; 3.05-3.55 (m, 10H)  
; 3.55-3.70 (m,1H) ; 6.90 (s,1H) ; 7.00 (s,1H); 7.15-7.45 (m,7H) ; 7.50 (s,2H) ; 8.50 (d,2H)  
; 11.15 (s,1H).

MS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 579.5

MS (ES<sup>-</sup>) m/z (M-H)<sup>-</sup> 577.6

**Preparation of starting materials.**

See Scheme 5 below for more details.

2N NaOH (510ml, 1.02mol) was added to a stirred solution of **A** (48.5g, 205mmol) in  
MeOH (550ml) and the resulting mixture heated at reflux for 2 hours. The RM was  
concentrated, acidified to pH 4 with 2N HCl and extracted with EtOAc (4 x 200ml). The  
25 combined organics were washed with brine (3 x 150ml), dried (MgSO<sub>4</sub>) filtered and  
evaporated to give **B** as a cream powder 40.3g (95%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 1.66 (s,6H) ; 7.55 (m,2H) ; 8.20 (m,2H).

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-Tetramethyluronium Hexafluoro-Phosphate (89.0g, 290mmol) was added portionwise to a stirred, cooled (0°C) solution of **B** (40.3g, 192mmol) in DMF (300ml) and Diethylamine (300ml). The resulting mixture was left to warm to RT and stir 70 hours. DMF was removed in vacuo and the residues redissolved in EtOAc (500ml), washed with water (3 x 200ml), brine (2 x 200ml), dried MgSO<sub>4</sub>, filtered and evaporated.

The crudes were purified by flash chromatography on SiO<sub>2</sub> (600g, Merck 9385) eluting with 35% EtOAc / i - Hexane. Appropriate fractions were combined and evaporated to give **C** as yellow crystalline solid 44.2g (87%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.90 (m, 3H) ; 0.90-1.25 (m, 3H) ; 1.58 (s, 6H) ; 2.65-2.95 (m, 2H) ; 3.20-3.45 (m, 2H) ; 7.40 (m, 2H) ; 8.20 (m, 2H).

LCMS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 265.48 (UV 254nm 100%)

A solution of **C** (89.0g, 338mmol) in EtOH (2L) was treated with 10% Pd/C (50% wet) (10.0g) then stirred under H<sub>2</sub> (3 Bar) at RT for 3 hours. The RM was filtered through Celite (545) and evaporated to give **D** as a tan solid 65.5g (83%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.90 (m, 3H) ; 0.90-1.25 (m, 3H) ; 1.48 (s, 6H) ; 2.80-3.10 (m, 2H) ; 3.15-3.45 (m, 2H) ; 3.45-3.75 (bs, 2H) ; 6.60-6.70 (m, 2H) ; 6.90-7.05 (m, 2H).

MS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 235.61

N-Bromosuccinimide (18.24g, 102.6 mmol) was added portionwise to a stirred, cooled (0°C) solution of **D** (24.0g, 102.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (250 ml) and the mixture stirred for 2 hours. The RM was evaporated, the residues redissolved in EtOAc (200ml), washed with saturated NaHCO<sub>3</sub> (aq) (3 x 200ml), water (2 x 200ml), brine (200ml), dried MgSO<sub>4</sub>,

filtered and evaporated. The crudes were purified by flash chromatography on SiO<sub>2</sub> (500g, Merck 9385) eluting with 5% MeOH / CH<sub>2</sub>Cl<sub>2</sub>. Appropriate fractions were combined and evaporated to give E as a tan solid 30.4g (94.7%).

5 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.90 (m,3H) ; 0.90-1.25 (m,3H) ; 1.48 (s,6H) ; 2.80-3.10 (m,2H) ; 3.15-3.50 (m,2H) ; 3.80-4.20 (bs,2H) ; 6.72 (m,1H) ; 6.95 (m,1H) ; 7.25 (m,1H).

MS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 313.23, 315.26

10

A solution of E (15g, 48mmol) in conc HCl (48ml) was cooled to -10°C and to it was added dropwise a solution of NaNO<sub>2</sub> (3.97g, 57.5mmol) in water (24ml) such that the internal temperature remained < - 8°C. The resulting solution was left to stir for 1hr at this temperature before it was added dropwise to a solution of SnCl<sub>2</sub>.2H<sub>2</sub>O (53.0g, 235mmol) in conc HCl (36.5ml) at -12°C such that the internal temperature remained < - 10°C. The mixture was stirred for 2 hours at -10°C then allowed to warm to 10°C before it was quenched into water (600ml), neutralised with solid NaHCO<sub>3</sub>, filtered and extracted with EtOAc (3 x 400ml). The organics were dried (MgSO<sub>4</sub>), filtered and evaporated to a yellow oil. This was treated with 1M HCl/Et<sub>2</sub>O and dried to give the HCl salt of F as a free  
15  
20 flowing white powder 14.7g (84.4%)

25

<sup>1</sup>H NMR (300MHz, DMSO-D<sub>6</sub>) 0.50-0.85 (m,3H) ; 0.85-1.10 (m,3H) ; 1.40 (s,6H) ; 2.70-3.00 (m,2H) ; 3.00-3.40(m,2H) ; 7.00-7.10 (m,1H) ; 7.10-7.20(m, 1H) ; 7.20-7.30 (m,1H).

LCMS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 328.3, 330.3 (UV 254nm 95%)

**Preparation of starting materials**

See Scheme 6 below for more details.

n-BuLi (1.6M in Hexanes) (100ml, 160mmol) was added dropwise to a stirred, cooled (-78°C) solution of 5-Bromoxylene (21.73ml, 160mmol) in THF (235ml) and Et<sub>2</sub>O (235ml) such that the internal temperature remained < -65°C. The resulting yellow suspension was allowed to stir for 1.25 hours before it was added via a cannula to a stirred, cooled (-78°C) solution of  $\gamma$ -Butyrolactone (14.7ml, 192mmol) in THF (180ml) such that the internal temperature remained < -70°C. The mixture was then stirred at this temperature for a further 5 hours, quenched with saturated NH<sub>4</sub>Cl (200ml) and extracted with Et<sub>2</sub>O (3 x 100ml). The combined organics were washed with brine (2 x 100ml), dried (MgSO<sub>4</sub>), filtered and concentrated to a yellow oil. This was then purified by chromatography on SiO<sub>2</sub> (Merck 9385) eluting with 45% EtOAc / i - Hexane to give **G** as a pale yellow oil 15.74g(60%).

15

<sup>1</sup>H NMR (300MHz, DMSO-D<sub>6</sub>) 1.70 (q, 2H); 2.30 (s, 6H); 2.98 (t, 2H); 3.42 (q, 2H); 4.43 (t, 1H); 7.22 (s, 1H); 7.52 (s, 2H).

20

Diethyl Azodicarboxylate (22.5ml, 143mmol) was added dropwise to a stirred, cooled (-5°C) solution of **G** (24.0g, 124mmol), Phthalimide (20.0g, 136mmol) and Triphenylphosphine (36.0g, 136mmol) in THF (450ml) such that the internal temperature remained < 0°C. The RM was stirred for 1hr at this temperature, diluted with EtOAc (600ml) and washed with water (250ml) and brine (250ml). The organics were then dried (MgSO<sub>4</sub>), filtered and concentrated to a yellow semi-solid. The crudes were purified by chromatography on SiO<sub>2</sub> (Merck 9385) eluting with 25% EtOAc / i - Hexane to give **H** as a white powder 13.3g (34%).

25

<sup>1</sup>H NMR (300MHz, DMSO-D<sub>6</sub>) 1.80-2.00 (m, 2H); 2.28 (s, 6H); 3.03 (t, 2H); 3.62 (t, 2H); 7.22 (s, 1H); 7.47 (s, 2H); 7.70 7.90 (m, 4H).

30

BF<sub>3</sub>.Et<sub>2</sub>O (30ml) was added to a stirred solution of **F** (27.0g, 74mmol) and **H** (24.4g, 77mmol) in AcOH (450ml) and the resulting mixture heated at 90°C for 48 hours. The RM was evaporated to dryness and the residues treated with saturated NaHCO<sub>3</sub> (100ml). The resulting solids were collected by filtration, triturated with MeOH/CHCl<sub>3</sub> and re-filtered.

5 The filtrates were concentrated to give **I** as an off-white powder 36g (79%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.75 (m, 3H); 1.00-1.15 (m, 3H); 1.54 (s, 6H); 2.25 (s, 6H); 2.80-2.95 (m, 2H); 3.24-3.40 (m, 2H); 3.15-3.23 (m, 2H); 3.80-3.90 (m, 2H); 6.80 (s, 1H); 7.06 (s, 2H); 7.12 (s, 1H); 7.45 (s, 1H); 7.55-7.70 (m, 4H); 8.02 (s, 1H).

10 LCMS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 613.9, 615.9 (UV 254nm 100%)

A solution of **I** (42.0g, 68mmol) in MeOH (1000ml) and Et<sub>3</sub>N (10ml) was treated with 10% Pd/C (10.0g) and stirred under H<sub>2</sub> (2 Bar) for 48 hours. The catalyst was removed by  
15 filtration through Celite (545) and the filtrates evaporated. The residues were redissolved in EtOAc, washed with water, dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give **J** as a yellow foam 32.2g (88%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) 0.60-0.80 (m, 3H); 1.05-1.25 (m, 3H); 1.60 (s, 6H); 2.30 (s, 6H); 2.85-3.05 (m, 2H); 3.20-3.50 (m, 4H); 3.90-4.00 (m, 2H); 6.85 (s, 1H); 6.95-7.05 (m, 1H); 7.12 (s, 2H); 7.20-7.35 (m, 1H + CHCl<sub>3</sub>); 7.55-7.7 (m, 3H); 7.70-7.80 (m, 2H); 8.00 (s, 1H).

LCMS (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> 536.59 (UV 254nm 100%)

25 LCMS (ES<sup>-</sup>) m/z (M-H)<sup>-</sup> 534.58 (UV 254nm 100%)

Hydrazine Hydrate (40ml, 192mmol) was added to a stirred solution of **J** (28g, 52.3mmol) in a mixture of MeOH (200ml) and CH<sub>2</sub>Cl<sub>2</sub> (200ml) and stirred for 48 hours at RT. A further portion of Hydrazine Hydrate (40ml) was added and stirring continued for  
30 another 24 hours. The RM was filtered, washed with saturated NaHCO<sub>3</sub> (4 x 150ml), brine



(2 x 100ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. The crudes were purified by flash chromatography on  $\text{SiO}_2$  (Merck 9385) eluting with EtOAc followed by 10% MeOH /  $\text{CH}_2\text{Cl}_2$  to give **K** as a pale yellow foam 17.1g(80.6%).

5  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 0.60-0.80 (m,3H) ; 1.05-1.25 (m,3H) ; 1.60 (s,6H) ; 1.76 (s,2H +  $\text{H}_2\text{O}$ ) ; 2.38 (s,6H) ; 2.80-3.12 (m,6H) ; 3.25-3.45 (m, 2H) ; 7.00 (s,1H) ; 7.02-7.07(m,1H) ; 7.17 (s,2H) ; 7.25-7.35 (m,1H) ; 7.42 (s,1H) ; 8.12 (s,1H).

LCMS ( $\text{ES}^+$ )  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  406.56 (UV 254nm 100%)

10 LCMS ( $\text{ES}^-$ )  $m/z$  ( $\text{M}-\text{H}$ ) $^-$  404.57 (UV 254nm 100%)

Diphenyl cyanocarbonimide (1.5g, 6.3mmol) was added to a stirred solution of **K** (1.5g, 3.7mmol) in IPA and the mixture stirred 18 hours at RT. The RM was concentrated in vacuo and the residues redissolved in EtOAc (150ml). The organics were washed with  
15 saturated  $\text{NaHCO}_3$  (3 x 70ml) , brine (2 x 75ml) , dried ( $\text{MgSO}_4$ ) , filtered and evaporated. The crudes were purified by flash chromatography on  $\text{SiO}_2$  (Merck 9385) eluting with a gradient 0 - 5% MeOH /  $\text{CH}_2\text{Cl}_2$  to give **L** as an off-white foam 1.9g(95.4%).

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 0.60-0.80 (m,3H) ; 1.00-1.20 (m,3H) ; 1.55(s,6H) ; 2.35  
20 (s,6H) ; 2.75-3.20 (m,2H) ; 3.10 -3.45 (m, 4H) ; 3.60-3.75 (m,2H) ; 6.30-6.45 (m,1H) ; 6.67-6.80 (m,2H); 7.00-7.50 (m,9H) ; 8.18 (s,1H).

MS ( $\text{ES}^+$ )  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  550.36

MS ( $\text{ES}^-$ )  $m/z$  ( $\text{M}-\text{H}$ ) $^-$  548.30, 454.38

25

1,1 Bis(methylthio)-2-nitroethylene (515mg,3.1mmol) was added to a stirred solution of **K** (1.1g, 2.72 mmol) in  $\text{CH}_3\text{CN}$  (70ml) and heated at reflux for 18 hours. The RM was concentrated in-vacuo and the crudes purified by chromatography on  $\text{SiO}_2$  (Merck 9385), eluting with 5% MeOH /  $\text{CH}_2\text{Cl}_2$  to give **M** as a yellow foam 1.4g(98%).

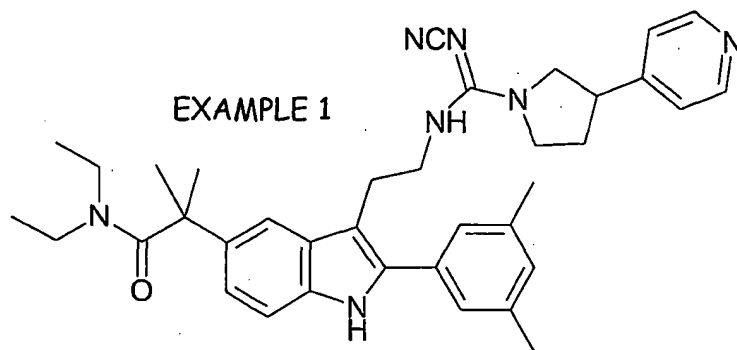
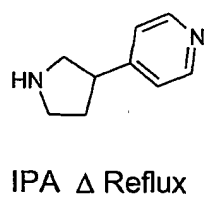
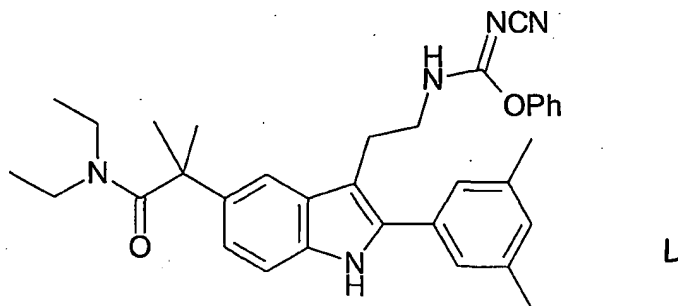
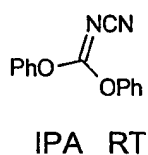
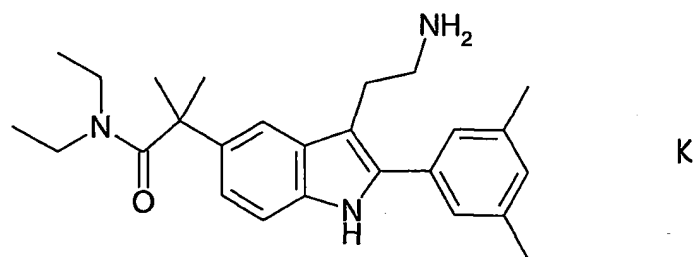
30

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ) 0.60-0.80 (m, 3H); 1.05-1.25 (m, 3H); 1.60 (s, 6H);  
2.38 (s, 6H); 2.80-3.05 (m, 2H); 3.25-3.50 (m, 4H); 3.68 (q, 2H); 6.42 (s, 1H); 7.05 (s, 1H)  
; 7.06-7.15 (m, 3H); 7.32 (d, 1H); 7.45 (s, 1H); 8.11 (s, 1H).

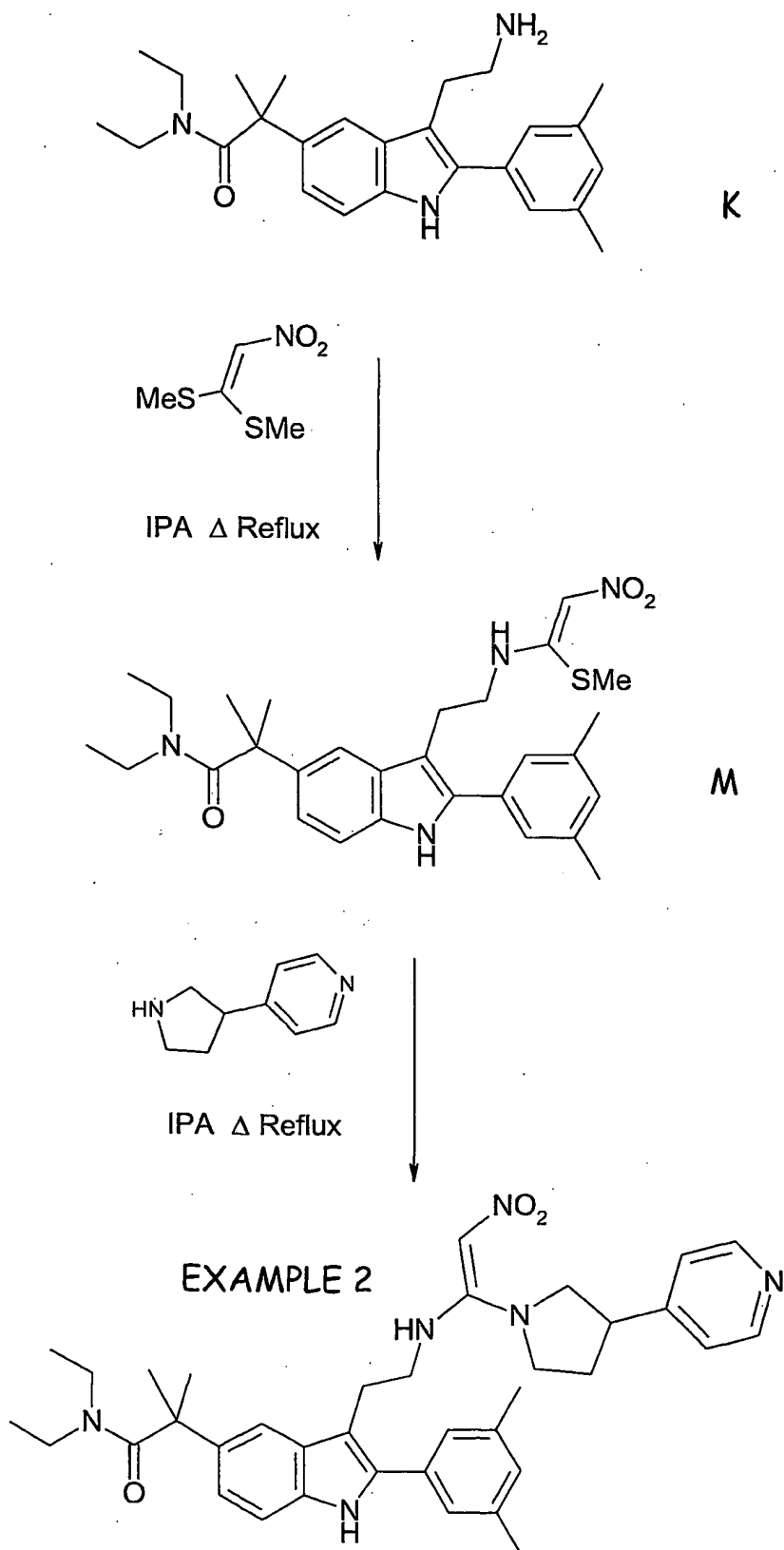
5 MS ( $\text{ES}^+$ )  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  523.44

MS ( $\text{ES}^-$ )  $m/z$  ( $\text{M}-\text{H}$ ) $^-$  521.49

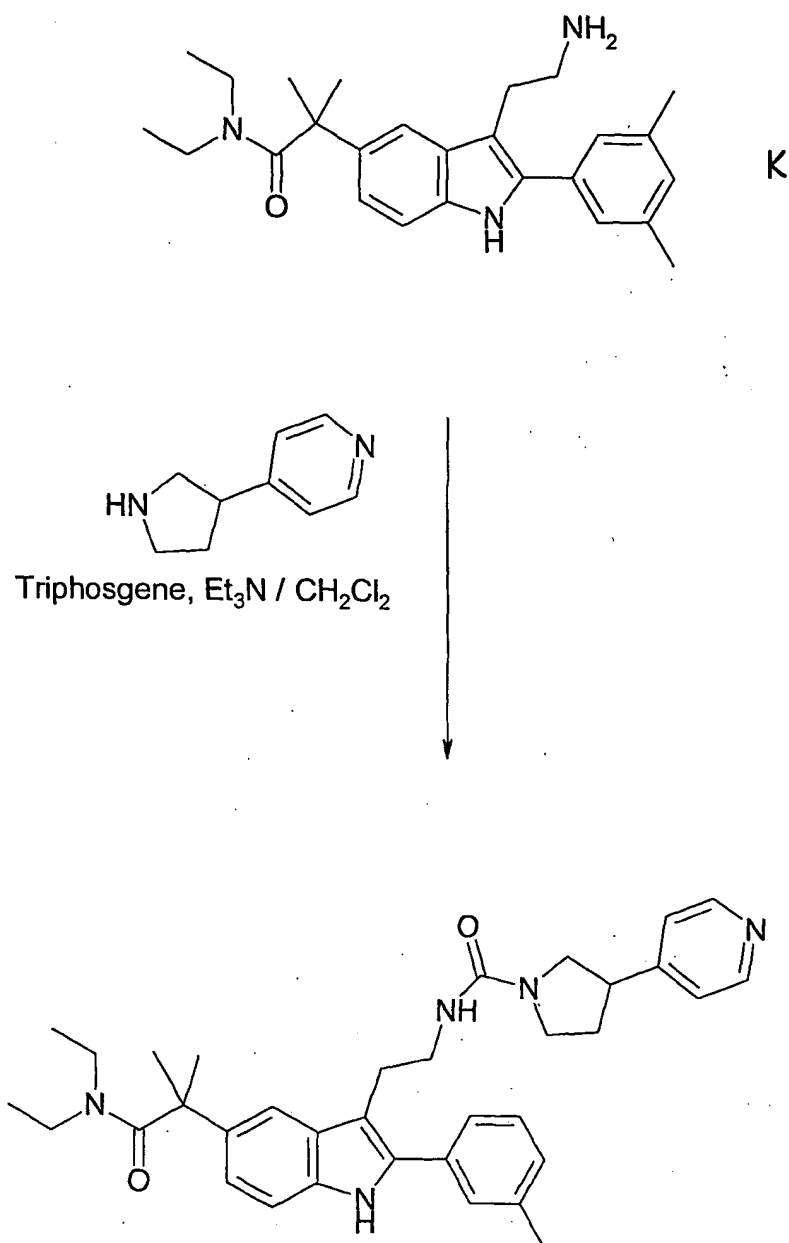
## Scheme 1



## Scheme 2

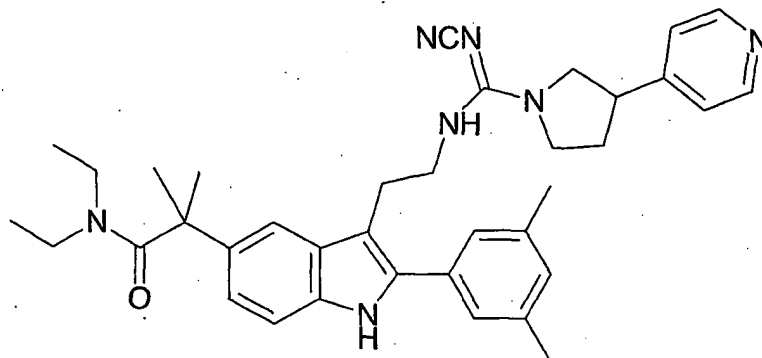


## Scheme 3



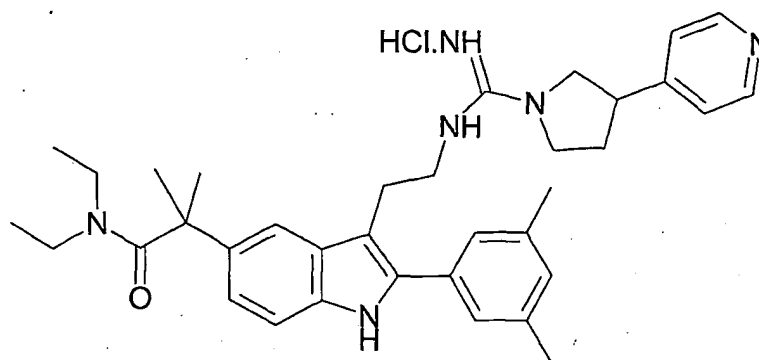
## EXAMPLE 3

## Scheme 4



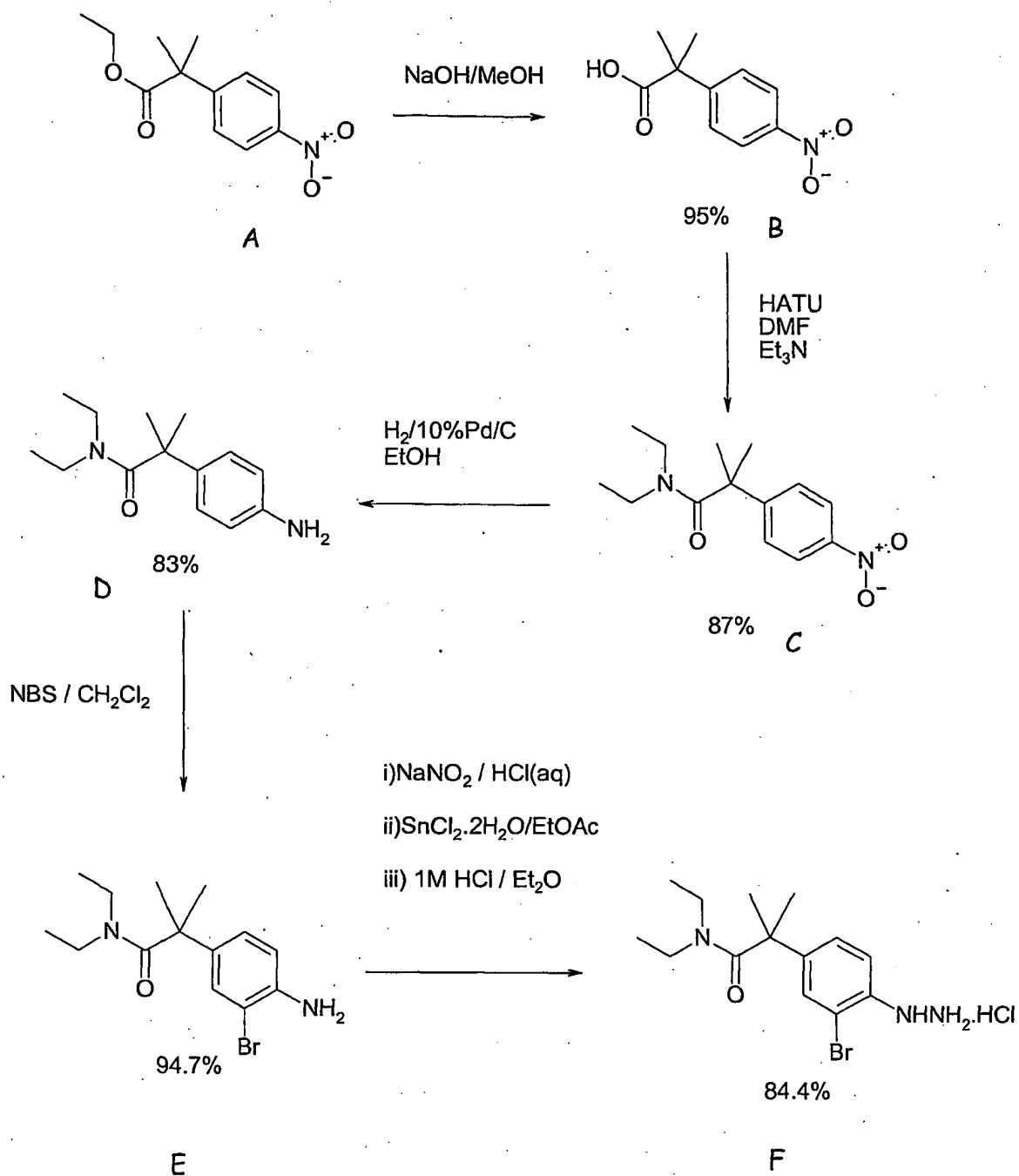
## EXAMPLE 1

2N HCl / MeOH  
60°C

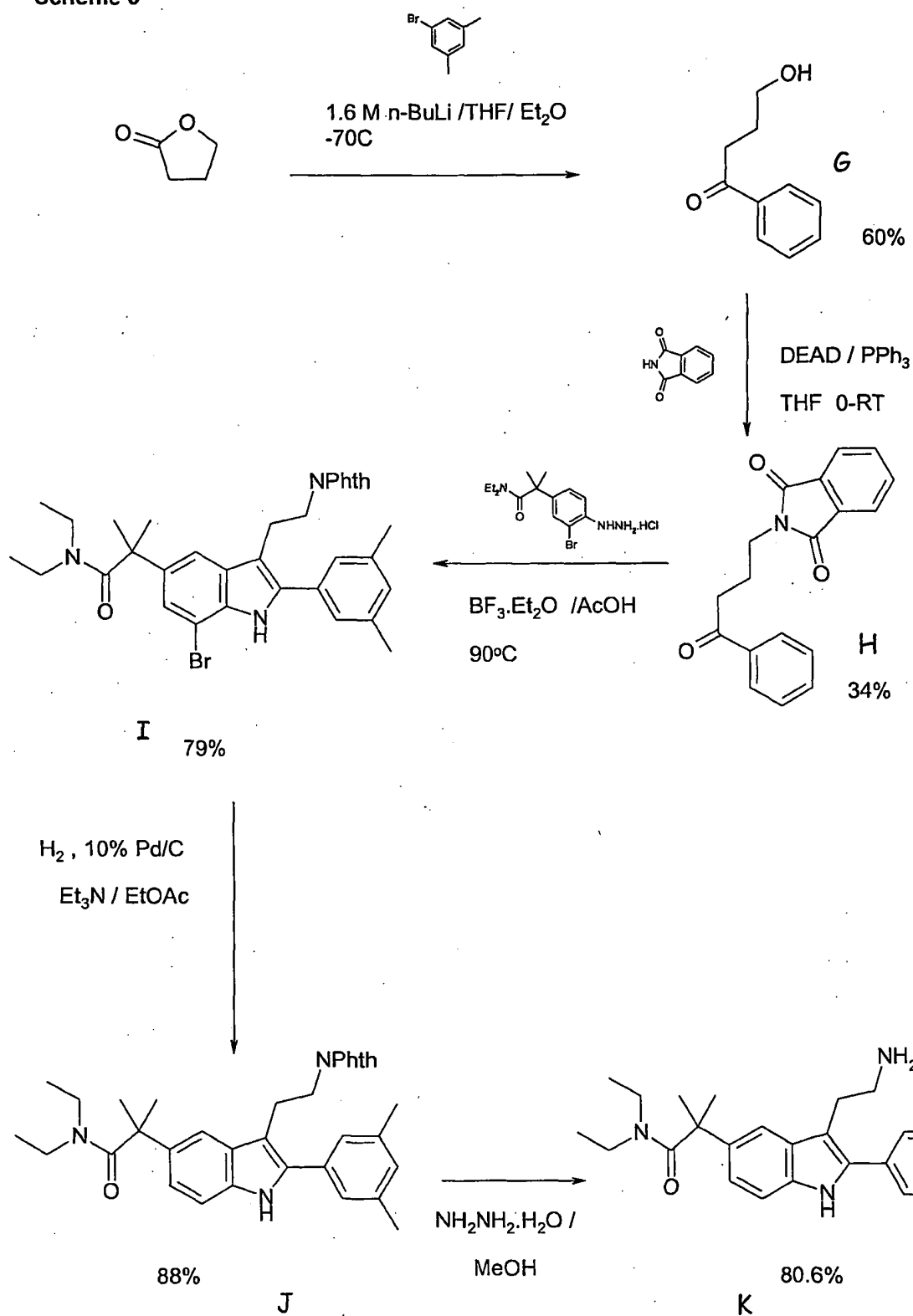


## EXAMPLE 4

Scheme 5



### Scheme 6





### THERAPEUTIC USES

Compounds of formula I are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of formula I can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of  $0.1\text{mgkg}^{-1}$  to  $30\text{mgkg}^{-1}$  (preferably,  $5\text{mgkg}^{-1}$  to  $20\text{mgkg}^{-1}$ ) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

The following illustrate representative pharmaceutical dosage forms containing a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof (hereafter referred to as "compound X"), for use in humans.

5

(a)

<u>Tablet I</u>	<u>mg/tablet</u>
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

10

(b)

<u>Tablet II</u>	<u>mg/tablet</u>
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

<u>Tablet III</u>	<u>mg/tablet</u>
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

<u>Capsule</u>	<u>mg/capsule</u>
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

<u>Injection I</u>	<u>(50 mg/ml)</u>
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

- 5 Buffers, pharmaceutically acceptable cosolvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl  $\beta$  cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for  
 10 reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's  
 15 risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are:  
 20 prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

## ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following *in vitro* assays.

### 5 Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl  
10 buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
- 15 3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC<sub>50</sub> of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

- 20 Compounds according to the present invention have activity at a concentration from 1nM to 5 µM.

### Binding Assay Using Human GnRH Receptor

- 25 Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC<sub>50</sub> which is the compound concentration required to inhibit the specific binding of [<sup>125</sup>I]buserelin to GnRH receptors by 50%. [<sup>125</sup>I]Buserelin (a  
30 peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

### Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as  
5 demonstrated by a reduction in GnRH-induced LH release.

### Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male  
10 rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12  
hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary  
glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS).  
The glands are further processed by:-

- 15 1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three  
successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2%  
20 hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a  
water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed  
to settle for 3 to 5 minutes;
- 25 7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Resuspension of the cells in culture medium of DMEM containing 0.37% NaHCO<sub>3</sub>,  
10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1%  
glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the  
30 collagenase and hyaluronidase;

10. Pooling of the cell suspensions and dilution to a concentration of  $3 \times 10^5$  cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO<sub>2</sub>/95% air atmosphere at 37°C for 3 to 4 days

5    Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

- 10   1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% NaHCO<sub>3</sub>, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

15

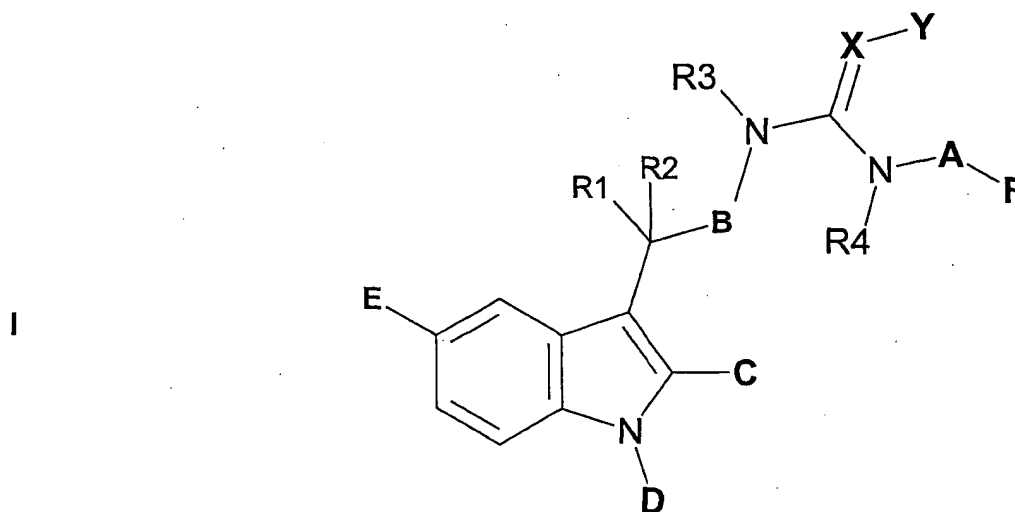
Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

20

- Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000.x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine
- 25   whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 µM.

**CLAIMS:**

1. A compound of formula I or a pharmaceutically acceptable salt or solvate thereof



For A, either:-

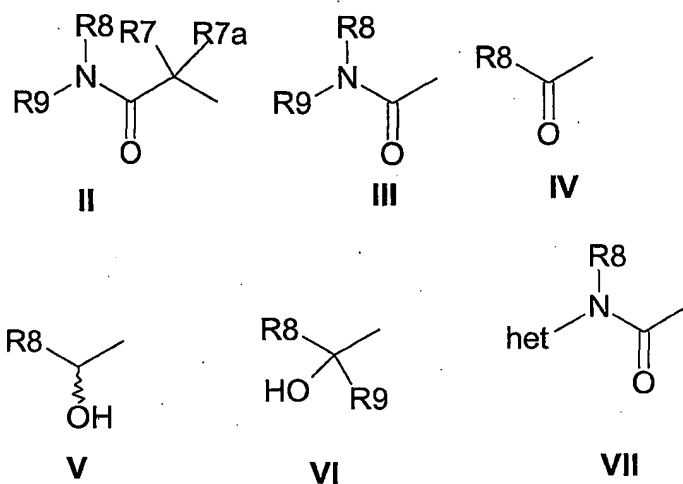
- (i) A represents a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or  $-R-Ar-R'$ , where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl; or
- (ii) the structure N-A(-R4) represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S, N-A(-R4) being optionally substituted;

B represents a bond or optionally substituted C1 to C5 alkylene;

C represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR<sub>5</sub>R<sub>6</sub>; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen;

D represents hydrogen; optionally substituted C1 to C8 alkyl; or  $(CH_2)_b-R$ , wherein R represents C3 to C8 cycloalkyl;

E is selected from an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; **II**; **III**; **IV**; **V**; **VI** and **VII**



wherein het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

F is optionally substituted and represents phenyl or a 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

For X and Y, either:-

(iii) X represents N and Y represents CN or H; or X represents CH and Y represents  $NO_2$ ; or

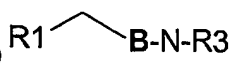
(iv) X-Y represents O;

For R1 and R2, either:-

(v) R1 and R2 are independently selected from hydrogen and optionally substituted C1 to C8 alkyl; or



(vi) R1 and R2 together represent carbonyl; or

(vii)  represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, and R2 meets the definition in option (v);

5

R3 meets the definition in option (vii) or represents hydrogen or optionally substituted C1 to C8 alkyl;

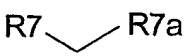
R4 meets the definition in option (ii) or represents hydrogen or optionally substituted C1 to C8 alkyl;

10

R5 and R6 are independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

15 For R7 and R7a, either:-

(viii) R7 and R7a are independently selected from H or optionally substituted C1 to C8 alkyl; or

(ix)  represents an optionally substituted 3 to 7-membered cycloalkyl ring;

20

For R8 and R9, either:-

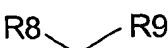
(x) R8 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; -R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and

25

R9 is selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl; or

(xi) wherein **E** represents structure **II** or **III**, NR8(-R9) represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

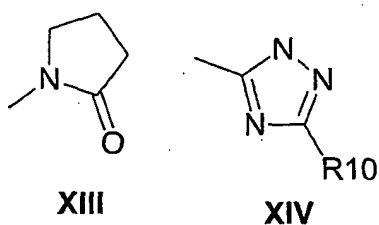
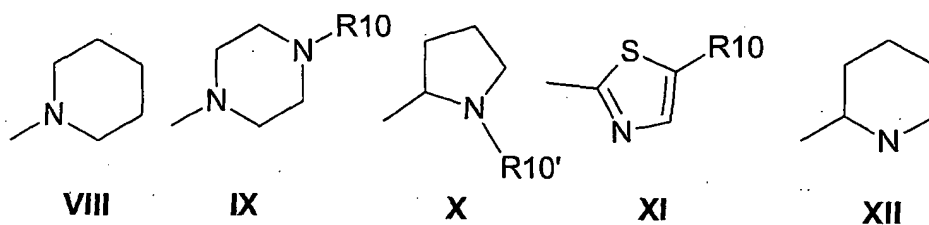
(xii) wherein **E** represents structure **VI**,

5  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

b represents zero or an integer from 1 to 6.

10

2. The compound of claim 1, wherein **F** is optionally substituted and represents pyridyl, **VIII**, **IX**, **X**, **XI**, **XII**, **XIII** or **XIV**



15

wherein

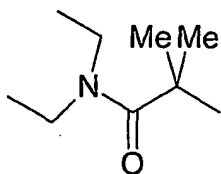
R10 represents hydrogen; optionally substituted C1 to C8 alkyl; OH; halogen; CN; C1 to C8 alkoxy; or CF<sub>3</sub>; and

R10' represents hydrogen or optionally substituted C1 to C8 alkyl.

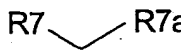
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3. The compound of claim 1 or 2, wherein, **E** represents

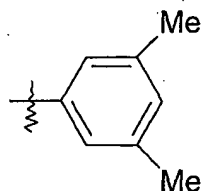
(a)



wherein Me represents methyl; or

- 5 (b) structure II, wherein  represents cyclopropyl or cyclobutyl.

4. The compound of any preceding claim, wherein C represents



- 10 wherein Me represents methyl.

5. The compound of any preceding claim, wherein X represents CH and Y represents NO<sub>2</sub>.
- 15 6. The compound of any one of claims 1 to 4, wherein X represents N and Y represents CN.
7. The compound of any one of claims 1 to 4, wherein X and Y represent O.
- 20 8. The compound of any preceding claim, wherein R1 and R2 each represent H and B represents C1 alkylene.
9. The compound of claim 1, wherein the compound is selected from  
2-(2-(3,5-dimethylphenyl)-3-{2-[(2-nitro-1-{[2-(4-

pyridinyl)ethyl]amino} ethenyl)amino]ethyl}-1H-indol-5-yl)-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[2-(4-pyridinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[2-(2-pyridinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[2-(1-imidazolyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[2-(3,5-dimethylphenyl)-3-(2-{[(phenethylamino)carbonyl]amino}ethyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[2-(3,5-dimethylphenyl)-3-(2-{[(4-pyridinyl)ethyl]amino}carbonyl]amino}ethyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[3-(4-methylpiperazino)propyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[2-(2-piperidinyl)ethyl]amino}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-[2-{[(cyanoimino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl]amino}ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-2{-[[(cyanoimino){[2-(4-pyridinyl)ethyl]aminomethyl}methyl]amino]ethyl}-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-[2-[(2-nitro-1-((3-(4-pyridinyl)-pyrrolidin-1-yl)ethenyl)amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-[2-((carbonyl)[3-(4-pyridinyl)-pyrrolidin-1-yl]amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide;

2-[3-[2-(((imino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl)amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-N,N-diethyl-2-methylpropanamide; and

2-[3-[2-(((cyanoimino)[3-(4-pyridinyl)-pyrrolidin-1-yl]methyl)amino)ethyl]-2-(3,5-dimethylphenyl)-1H-indol-5-yl]-1-cyclopropylcarboxylic acid-diethylamide.

10. A compound according to any preceding claim for use as a medicament.

11. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable diluent or carrier.

12. Use of a compound according to any one of claims 1 to 9, in the manufacture of a medicament, for antagonising gonadotropin releasing hormone activity.

13. Use of a compound according to any one of claims 1 to 9, in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

14. Use of a compound according to any one of claims 1 to 9, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

15. The use according to claim 14, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the

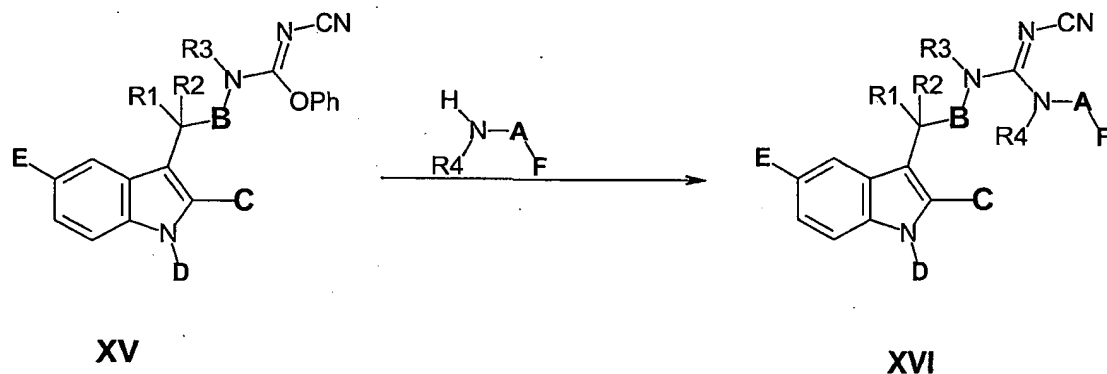
uterus.

16. The use according to claim 15, wherein the sex hormone dependent cancer is selected from prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe  
adenoma.

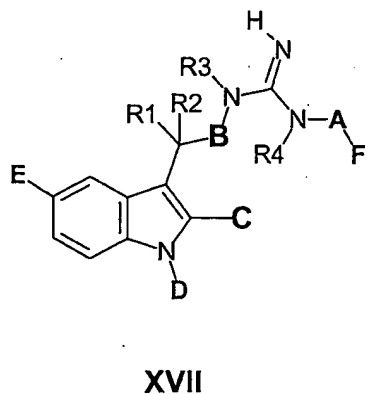
17. A method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering to the patient a compound according to any one of claims 1 to 9.

18. A process of producing a compound according to any one of claims 1 to 8, wherein the process comprises a reaction step selected from steps (a) to (e):-

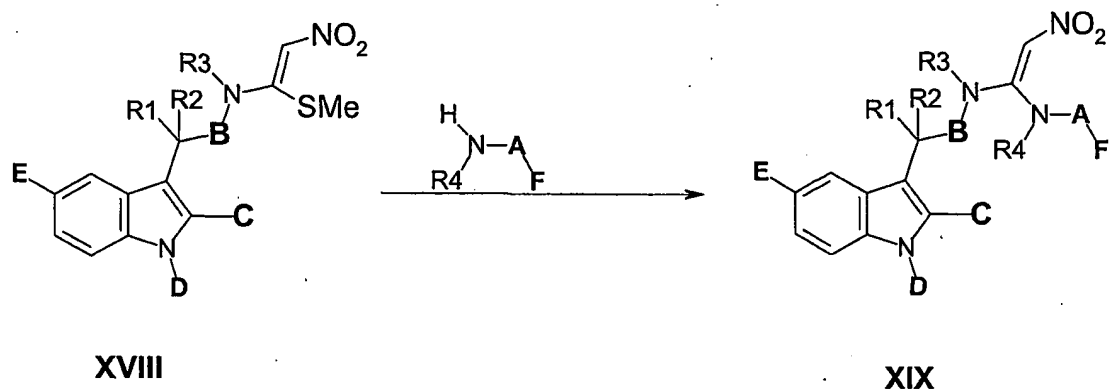
(a) Reaction of **XV** as follows



(b) Cleavage of the CN group of **XVI** in the presence of acid to produce **XVII**

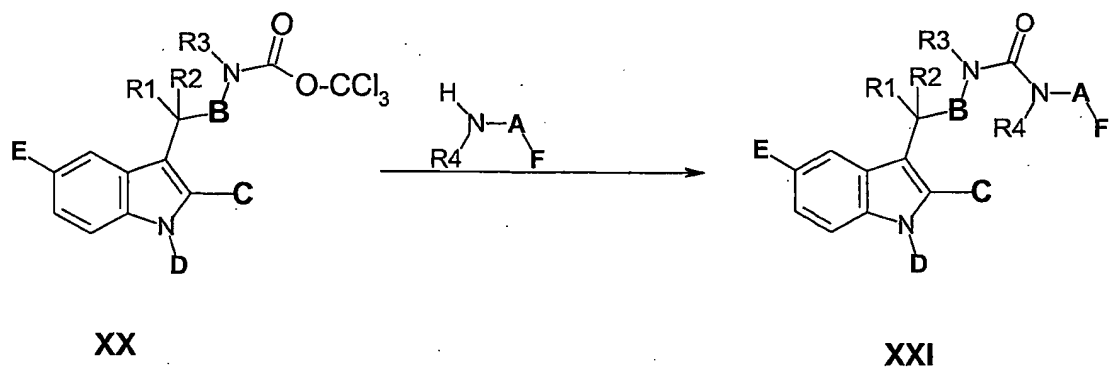


(c) Reaction of **XVIII** as follows

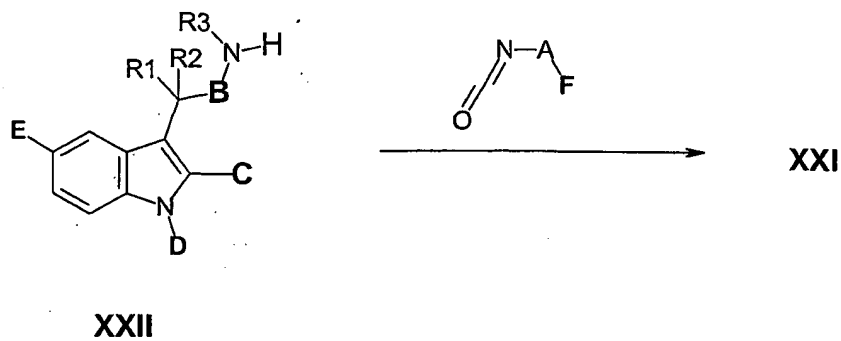


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(d) Reaction of **XX** as follows



(e) Reaction of **XXII** as follows



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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/00679

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/404 A61P5/02 C07D409/12 C07D209/16  
C07D417/12 C07D403/12 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 21435 A (MERCK & CO., INC.) 19 June 1997 (1997-06-19) cited in the application * complete document, in particular page 3 and example 6.3, 6.4 and 12.2 *	1,10-12
A	WO 97 21703 A (MERCK & CO., INC.) 19 June 1997 (1997-06-19) cited in the application claims	1,10-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 May 2002

Date of mailing of the international search report

31/05/2002

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Van Bijlen, H



## INTERNATIONAL SEARCH REPORT

Int lonal Application No

PCT/GB 02/00679

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